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NEW DEVELOPMENTS IN ALKALOID CHEMISTRY

Convened and Edited by

A. R. BATTERSBY

University of Bristol, England

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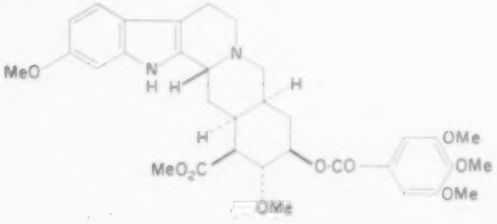
INTRODUCTION

RESEARCH ON ALKALOIDS, IN RETROSPECT AND IN PROSPECT

A. R. BATTERSBY
Department of Organic Chemistry, The University, Bristol

IN considering an introduction to this Symposium on New Developments in Alkaloid Chemistry, it is right that one's mind's eye should be cast back to look at the contribution which research on alkaloids has made to the development and vigour of organic chemistry. With pure alkaloids available almost from the start of our science, and with several of them having useful medicinal properties, it is not surprising that they attracted the interest of many great chemists of those times. Indeed, during the classical period of organic chemistry, outstanding contributions to the chemistry of these plant bases were made by Pictet, Perkin, Robinson, Pschorr, Wieland, Willstätter, Karrer, Windaus, Schöpf, Späth and Leuchs. These men were followed, or joined, by many eminent chemists in the 1925–1945 period. The influence which their efforts has had upon organic chemistry as a whole is immense. Perkin's attempts to synthesize quinine which accidentally gave rise to the synthetic dye industry; Willstätter's work on the tropane alkaloids which led to many valuable discoveries including cyclo-octatetraene; Pschorr's phenanthrene synthesis as a direct result of structural work on morphine; the development of important ideas concerning biosynthesis which grew alongside, and in many cases as a result of, increasing knowledge of the structure of alkaloids. The list could be extended but it will suffice to mention the wealth of knowledge concerning properties and reactions which these studies added to the harvest from other fields. Some decline in research effort on the alkaloids occurred during the ten years or so before the middle nineteen forties, but this has been followed by a great expansion in interest and activity which at the present time shows no signs of slackening. This has occurred partly because many of the large pharmaceutical companies have joined in the search for new alkaloids and in the study of their structures, no doubt stimulated by the isolation[1] of reserpine (I). But this effort has been matched by an upsurge of interest and enthusiasm in many academic laboratories where chemists have been attracted by the fascinating problems of structure, stereochemistry, and synthesis in this field.



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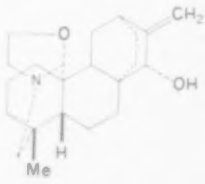

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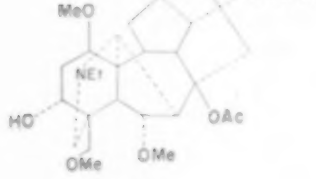
[1] J. M. Mueller, E. Schlittler and H. J. Bein, *Experientia* **8**, 338 (1952).

With all this activity directed towards the alkaloids, it is satisfying to find that this period has been an outstandingly successful one. In giving examples of the progress achieved, it must be stressed that the following pages are intended to be illustrative rather than in any way to give a complete survey. Indeed, if such a survey were attempted, the introduction might well fill several issues.

Several groups of alkaloids of unknown nature were left to us by earlier generations of chemists and these groups represented some of the major unsolved structural problems in tl.e field. Spectacular advances in knowledge of these groups have been made during the past ten years or so. In general, the structures revealed are too complex to have been attacked with any real hope of success with the knowledge, techniques, and equipment of say the nineteen thirties. For example, there has been a complete transformation in our understanding[2] of the diterpene alkaloids isolated from *Aconitum*, *Delphinium*, and *Garrya* species. Two papers in this Symposium deal with the atisine-type alkaloids of which atisine itself has the structure (II). Many fascinating researches[3] have uncovered the structures of those diterpene alkaloids which have



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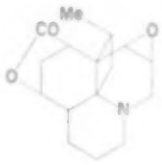

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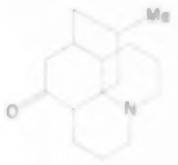

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rearranged skeletons; aconitine (III) has been a particularly interesting example. In 1956, not a single structure could be given for any of the *Lycopodium* alkaloids but, among others, the structures of annotinine[4] (IV) and lycopodine[5] (V) are now known, and a very satisfying biogenetic pattern is emerging in this group of bases.[6] In the steroidal group of alkaloids, there has been much interest in conessine both structurally[7] and in connexion with the C-18 functionalization of steroids.[8] Also many potentially useful new steroidal alkaloids, including curarizing agents, have been isolated (see p. 126). Rearranged steroidal skeletons have been found in the *Veratrum* alkaloids which extend in complexity from veratramine[9] (VI) to cevine[10] (VII) and its esters. The work on cevine and its relatives is a striking example of the way a difficult structure

[2] Reviewed by K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturstoffe* **16**, 26 (1958).
[3] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Letters* No. 2, 15 (1959). F. W. Bachelor, R. F. C. Brown and G. Büchi, *Ibid.* No. 10, 1 (1960); K. Wiesner, D. L. Simmons and L. R. Fowler, *Ibid.* No. 18, 1 (1959), and references given therein.
[4] K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis, *Tetrahedron* **4**, **87**, (1958).
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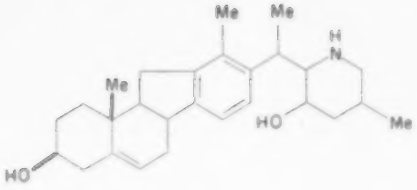
[8] E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.* **81**, 5209 (1959); G. Cainelli, M. L. Mihailovic, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **42**, 1124 (1959) and related papers; D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.* **82**, 2641 (1960).
[9] Ch. Tamm and O. Wintersteiner, *J. Amer. Chem. Soc.* **74**, 3842 (1952).
[10] D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia* **10**, 81 (1954); K. J. Morgan and J. A. Barltrop, *Quart. Rev.* **12**, 34 (1958); S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron* **7**, 47 (1959).



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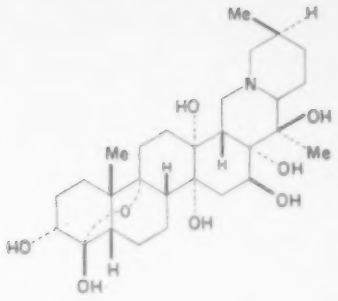

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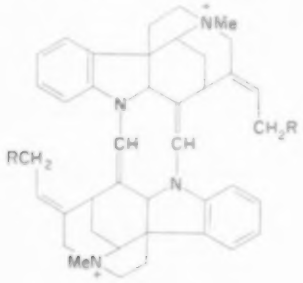
can be elucidated by degradation combined with the extensive use of physical methods and a full application of present knowledge of reaction mechanisms.

Because of their inaccessibility and awkward properties, the quaternary alkaloids of calabash curare have for long appeared in the literature as partial structures showing only fragments of the molecules. Recently, the structures of the key compounds, C-dihydrotoxiferine-I[11] (VIII; R = H) and toxiferine-I[11,12] (VIII; R = OH) have been determined and they are seen to be representatives of a new class of natural products, the dimeric indole alkaloids. With these structures settled, the way has been opened to further structures in this complex group of alkaloids. The Symposium includes an account of the work leading to the structure of the first crystalline calabash curare alkaloid to be isolated, C-curarine-I. Work is proceeding apace on other dimeric indole alkaloids, including geissospermine (see p. 113) in which the two "halves" are linked in a way different from that used in the calabash curare alkaloids.

There is little doubt that the direct X-ray crystallographic method for determination of structure will be used to a steadily increasing extent in natural product work. This is particularly so in the alkaloid field where the necessary heavy atom is so readily introduced. Already this technique has yielded the structures of the rearranged diterpene alkaloids of the lycoctonine type,[13] gelsemine[14] (IX) aspidospermine[15] (X), and



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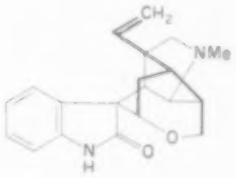

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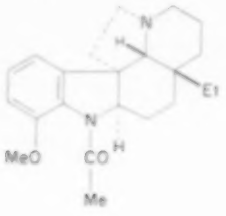
[11] K. Bernauer, H. Schmid and P. Karrer, *Helv. Chim. Acta* **41**, 1408 (1958); K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid and P. Karrer, *Ibid.* **41**, 2293 (1958); V. Boekelheide O. Ceder, T. Crabb, Y. Kawazoe and R. N. Knowles, *Tetrahedron Letters* No. 26, 1 (1960).
[12] A. R. Battersby and H. F. Hodson, *Proc. Chem. Soc.* 287 (1958). A. R. Battersby and H. F. Hodson, *J. Chem. Soc.* 786 (1960). For reviews see K. Bernauer, *Fortschr. Chem. Org. Naturstoffe* **17**, 184 (1959); A. R. Battersby and H. F. Hodson, *Quart. Rev.* **14**, 77 (1960).
[13] M. Przybylska and L. Marion, *Canad. J. Chem.* **34**, 185 (1956).
[14] F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Letters* No. 4, 1 (1959).
[15] J. F. D. Mills and S. C. Nyburg, *J. Chem. Soc.* 1458 (1960).

calycanthine[16] (XI). These bases have all been extensively studied by the degradative approach which, in two of the cases given, yielded virtually simultaneously the same structure as the X-ray method.



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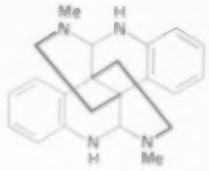

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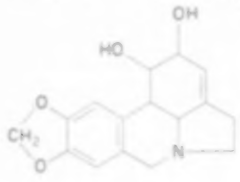
During this same period, new groups of alkaloids have been discovered, and other groups, if not completely new, have been so vastly extended as to have been transformed. This is true of the *Amaryllidaceae* alkaloids[17] where now nearly one hundred are known and the structures of many of them have been worked out. Representative examples are lycorine (XII), haemanthamine (XIII), galanthamine (XIV), and tazettine (XV). As knowledge of this group grew, a close structural relationship between the



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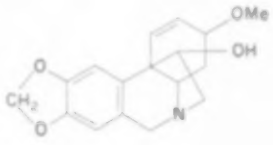

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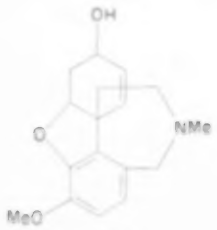

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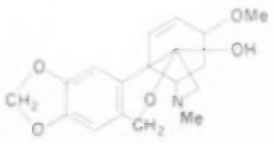
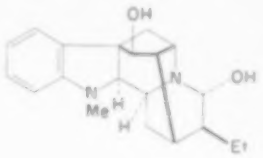


XV

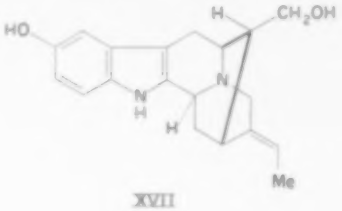
various members was recognized[18] and explained by a very satisfying and elegant theory[18] based upon phenolic coupling. Moreover, evidence from tracer experiments[19] gives the theory strong support. The number of pure *Rauwolfia* alkaloids has also multiplied to over thirty and in addition to reserpine (I), the structures of ajmaline[20] (XVI) and sarpagine[21] (XVII) are of interest in being tightly caged; closely related

[16] T. A. Harmor, J. M. Robertson, H. N. Shrivastava and J. V. Silverton, *Proc. Chem. Soc.* 78 (1960).
[17] W. C. Wildman, *The Alkaloids* (Edited by R. H. F. Manske) Vol. VI, p. 290. Academic Press, New York (1960).
[18] D. H. R. Barton and T. Cohen, *Festschrift Arthur Stoll* p. 117. Birkhauser Verlag, Basel (1957).
[19] A. R. Battersby, R. Binks and W. C. Wildman, *Proc. Chem. Soc.* 410 (1960); see also ref. 38.
[20] R. B. Woodward, *Angew. Chem.* **68**, 13 (1956); Sir R. Robinson, *Ibid.* **69**, 40 (1957) and references given therein; M. F. Bartlett, E. Schlittler, R. Sklar, W. I. Taylor, R. L. S. Amai and E. Wenkert, *J. Amer. Chem. Soc.* **82**, 3792 (1960).
[21] M. F. Bartlett, R. Sklar and W. I. Taylor, *J. Amer. Chem. Soc.* **82**, 3790 (1960) and references given therein.

structures have been found in the calabash curare group.[22] New alkaloidal types have been found in *Tabernathe iboga*[23] and *Voacanga africana*,[24] and the structure of ibogaine[23] (XVIII) shows the unusual seven-membered ring C which characterises this group of bases. Still further new types which lack the "tryptamine"side-chain have been isolated from *Aspidosperma* plants. Examples are uleine[25] (XIX) and ellipticine[26] (XX).

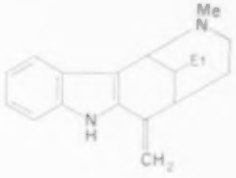


XVI

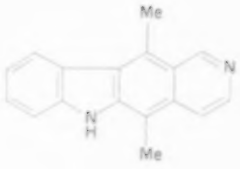


XVII

XVIII



XIX

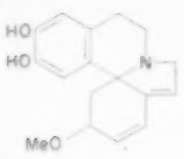


XX

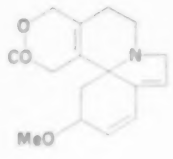
In the isoquinoline series, tremendous progress has been made in the *Erythrina* group[27] leading to many structure elucidations, including erysopine (XXI) and β-erythroidine[28] (XXII). Elsewhere in this series, new structural types are still appearing (see p. 42) and there has been much interest in the stereochemistry and synthesis of isoquinoline alkaloids. Thus the formula (XXIII) is now known to be a complete expression for emetine[29] and this knowledge has been used in a controlled synthesis of

[22] W. Arnold, W. von Philipsborn, H. Schmid and P. Karrer, *Helv. Chim. Acta* **40**, 705 (1957); A. R. Battersby and D. A. Yeowell, *Proc. Chem. Soc.* 17 (1961).
[23] M. F. Bartlett, D. F. Dickel and W. I. Taylor, *J. Amer. Chem. Soc.* **80**, 126 (1958) and earlier papers.
[24] D. Stauffacher and E. Seeback, *Helv. Chim. Acta* **41**, 169 (1958).
[25] G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.* **81**, 4434 (1959).
[26] S. Goodwin, A. F. Smith and E. C. Horning, *J. Amer. Chem. Soc.* **81**, 1903 (1959); R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, *Ibid.* **81**, 4434 (1959).
[27] Reviewed by V. Prelog, *Angew. Chem.* **69**, 33 (1957).
[28] Reviewed by V. Boekelheide and V. Prelog, *Progress in Organic Chemistry* (Edited by J. W. Cook) Vol. 3, p. 256. Butterworths, London (1955).
[29] A. R. Battersby, R. Binks and G. C. Davidson, *J. Chem. Soc.* 2704 (1959). A. R. Battersby and S. Garratt, *Ibid.* 3512 (1959); A. R. Battersby, R. Binks and T. P. Edwards, *Ibid.* 3474 (1960); A. Brossi, A. Cohen, J. M. Osbond, Pl. A. Plattner, O. Schnider and J. C. Wickens, *Ibid.* 3630 (1959); E. E. van Tamelen, P. E. Aldrich and J. B. Hester, *J. Amer. Chem. Soc.* **81**, 6214 (1959); Y. Ban, M. Terashima and O. Yonemitsu, *Chem. & Ind.* 568, 569 (1959).

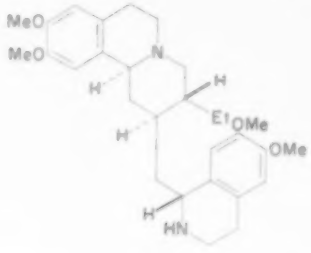
the Ipecacuanha alkaloids.[30] Also, several simple isoquinoline alkaloids, protoberberines (see p. 46), benzylisoquinolines, and benzophenanthridine alkaloids have been synthesized.



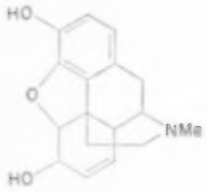
XXI



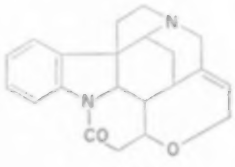
XXII



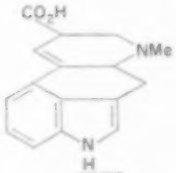
XXIII



XXIV



XXV



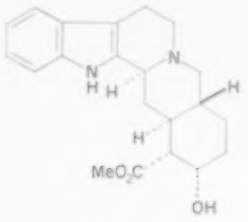
XXVI

At this point, the many brilliant syntheses of complex alkaloids accomplished during the period under review can be collected together. The syntheses of morphine[31] (XXIV), strychnine[32] (XXV), lysergic acid[33] (XXVI), and reserpine[34] (I) amply demonstrate the power of organic synthesis. Around the time these had been completed, Woodward listed[35] a number of objectives for synthesis which included yohimbine[36] (XXVII) and colchicine (XXVIII). Both these difficult objectives have now been reached (see p. 8 and ref. 37) and a synthesis of galanthamine (XIV), patterned on the proposed biosynthetic route, has been achieved.[38]

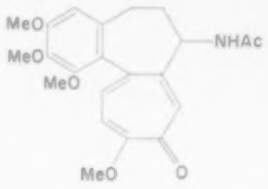
A major development over the past ten years or so has been the use of radioactive tracers in the study of alkaloid biosynthesis. Much is now known[39] about the biosynthesis of nicotine (XXVIII) the tropane alkaloids, morphine (XXIV) and its relatives, lysergic acid (XXVI), and many simpler structures such as the β-phenylethylamines. Colchicine, as might be expected, is proving to be excitingly unusual.[39] There is much still to be done, but it seems to me that the breakthrough has been made and that progress should now be rapid.

[30] A. R. Battersby and J. C. Turner, *J. Chem. Soc.* 1960, 717; references are given there to other syntheses in this field.
[31] M. Gates and G. Tschudi, *J. Amer. Chem. Soc.* **74**, 1109 (1952); D. Elad and D. Ginsburg, *Ibid.* **76**, 313 (1954).
[32] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Amer. Chem. Soc.* **76**, 4749 (1954); R. B. Woodward, *Experientia Suppl.* II (1955).
[33] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, R. G. Jones and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 5256 (1954).
[34] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).
[35] R. B. Woodward, *Perspectives in Organic Chemistry* (Edited by A. R. Todd) p. 155. Interscience, New York (1956).
[36] E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm and P. E. Aldrich, *J. Amer. Chem. Soc.* **80**, 5006 (1958).
[37] J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel and A. Eschenmoser, *Angew. Chem.* **71**, 637 (1959).
[38] D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.* 392 (1960).
[39] Forthcoming review by A. R. Battersby in *Quart. Rev.*

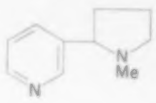
What of the future? There seems to be no sign that all the new structural types of alkaloids have been found. Many new alkaloids will be based upon known skeletons but completely new types are being steadily discovered and my hope and expectation



XXVI



XXVII



XXVIII

is that this will continue. Thus the prospect seems to be one of increased activity in surveying plants for alkaloids followed by a more rapid determination of the structures of the bases obtained. Without question there will also be a great effort put into the study of alkaloid biosynthesis. Synthesis in the laboratory presents many challenges and lycorine (XII), haemanthamine (XIII), and ajmaline (XVI) all have features which should attract skill and effort. If a still greater challenge is required, then aconitine (III) and cevine (VII) are available.

I hope that the foregoing paragraphs will have indicated the present flourishing state of alkaloid chemistry and also its bright future. It was these factors which suggested that a Symposium on alkaloids would be timely and welcome. We have been fortunate in securing contributions from many of the outstanding workers in this field and it should be mentioned that an equally strong "team" of different contributors was available. This is indeed a healthy state of affairs. If the present Symposium is judged to add something of value to organic chemistry, then further Symposia might well be arranged in the future so that contributions from other "teams" may be collected together. Comments will be welcomed.

Tetrahedron, 1961, Vol. 14, pp. 8 to 34. Pergamon Press, Inc. Printed in Northern Ireland

THE SYNTHESIS OF COLCHICINE

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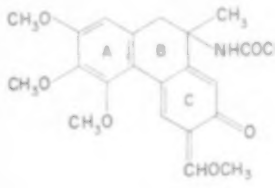
(*Received* 25 *November* 1960)

Abstract—A synthesis of the alkaloid colchicine (II) involving the operations III → IX → XIIIb → XIVb → XVIIIb → XXV → XXVII → XXVIII → V → XXXIV → XXXV → XXXVI → XXIX (XXIX → II) is described.[1]

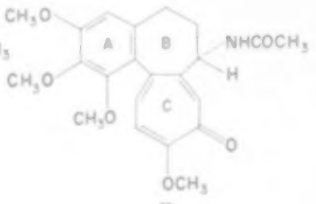
INTRODUCTION

COLCHICINE, the principal alkaloid of the autumn crocus (*Colchicum autumnale L.*) was isolated and characterized in the early part of the nineteenth century, and since then has been an object of study in the chemical as well as the biological and medical sciences.[2]

Of the early chemical investigators, Windaus is most prominent, his findings having led him to propose in 1924 a complete structure (I), based on a phenanthrene skeleton, for the alkaloid.[3] Some years later, Cook discovered that the central (B) ring was instead seven-membered;[4] and at about the same time, Dewar urged that the C-ring



I



II

might be better regarded as tropolonoid.[5] The proposed structure II was later confirmed by chemical means as well as by X-ray studies,[6] and more recently the absolute stereo-chemistry indicated in structure II was established.[7]

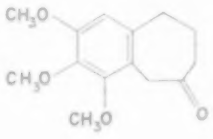
Historically, the use of the ancient drug *Colchicum* "is rooted in the myths and written records of ancient Egypt, India and Greece, and runs its course through the ages into the world of today."[8] Normally regarded as a highly poisonous substance, colchicine nevertheless serves as a medicinal agent. Apart from its long-standing use in the treatment of gout, the potential of colchicine as an anti-cancer agent is noteworthy.[9] The latter characteristic seems associated with the remarkable effect of the

[1] For a preliminary announcement of this work, see *J. Amer. Chem. Soc.* **81**, 6341 (1959).
[2] O. J. Eigsti and P. Dustin, Jr., *Colchicine*. The Iowa State College Press, Ames, Iowa (1955).
[3] A. Windaus, *Liebigs Ann.* **439**, 59 (1924).
[4] G. L. Buchanan, J. W. Cook and J. D. Loudon, *J. Chem. Soc.* 325 (1944).
[5] M. J. S. Dewar, *Nature, Lond.* **155**, 141 (1955).
[6] M. V. King, J. L. DeVries and R. Pepinsky, *Acta Cryst.* **5**, 437 (1952).
[7] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **38**, 2030 (1955).
[8] Reference 2, p. 1.
[9] e.g. Deacetyl-N-methylcolchicine (Demecolchicine) has been used in the treatment of granulocytic leukemia (*Chem. Engng. News* **37**, No. 41, 67 (1959).

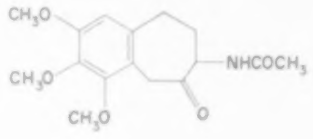
substance on cell division at the mitosis stage, a property which also renders colchicine of use in the study of cell replication mechanisms.

Although a relatively simple structure by present-day standards, and free from stereochemical complications, colchicine nevertheless has constituted for some time a serious problem in the field of total synthesis. The particular reasons for failure of the various attempts made during the past fifteen years are probably numerous and are not properly discussed here; but it may be safely stated that they were in general a consequence of the several unusual molecular features of colchicine, which individually would present no serious threat, but combined into a single structure, offer a unique challenge. During the latter half of 1959, sequences which constitute two total syntheses of the alkaloid, similar in principle but different in detail, were announced. The first report of success was made by Eschenmoser *et al.*[10], which disclosure was followed shortly by an announcement from this laboratory.[1]

Our own interest in colchicine centered around the problem of constructing tropolone rings in complex systems. In connection with the general problem of a total synthesis, we were led, in examining the state of colchicine chemistry in 1956, to the conclusion that 2,3,4-trimethoxy-benzocycloheptan-6-one (III) would serve well as a

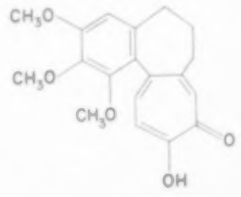


III



IV

starting point for synthetic studies. That being the case, the general requirements were twofold: (a) attachment of a tropolonoid C-ring to the 5,6-position of III, and (b) insertion of a nitrogen function at the 7-position. The second requirement might be faced first, and in that connection several attempts to convert the acetamido-trimethoxy-β-benzosuberone IV[11] to colchicine-like structures were made in this Laboratory, but without promise. Therefore, this implied order of events was abandoned, and efforts were made to transform ketone III to a specific key intermediate, the previously unknown desacetamidocolchiceine (V), into which the required nitrogen function



V

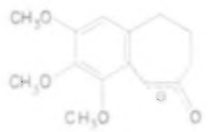
would be introduced subsequently. Thus, the basic concept of this synthetic program may be represented by the summarized sequence: III → V → II.

[10] J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel and A. Eschenmoser, *Angew. Chem.* **71**, 637 (1959).
[11] G. L. Buchanan and J. K. Sutherland, *J. Chem. Soc.* 2334 (1957).

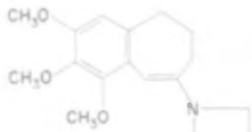
SYNTHESIS OF DESACETAMIDOCOLCHICEINE

Although a variety of methods for building up tropolone rings has become available during the past decade or so,[12] it appears that none of these is so general that it can be applied routinely to a given, complex case. Experiences of many other workers along with findings arising from the present investigation, have demonstrated forcibly that construction of a tricyclic tropolone of the colchicine type is beset with uncommon difficulty. As stated earlier, the immediate problem which confronted us was appending a third, tropolonoid C-ring to the selected starting material, the trimethoxy-β-benzosuberone (III).[13] This ketone was first prepared in 1951 by Rapoport and Campion[14], whose route starts with 3,4,5-trimethoxybenzaldehyde and proceeds through a number of standard operations. Subsequently, Eschenmoser and Rennhard reported that the same ketone results on application of an ingenious sequence of reductions to purpurogallin tetramethylether.[15,16] Later works have modified the purpurogallin approach, and at the present time a choice of reliable procedures is available.[17]

All of our projected and tested approaches involved using the anion (VI) (or an equivalent) of the trimethoxy-β-benzosuberone for establishment of a carbon–carbon bond at C-5. In agreement with published[18] and unpublished observations of other



VI

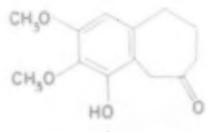


VII

workers, such alkylations are, almost without exception, futile; none, or only a small amount of the desired product is formed. In this Laboratory such attempts included treatment of anion VI with glyoxylic ester and nitroethylene, and, in the case of either VI or the pyrrolidine enamine VII (m.p. 93–97°),[19] with β-acetylacrylic ester and

[12] For a summary, see P. L. Pauson, *Chem. Rev.* **55**, 30 (1955).

[13] The Eschenmoser synthesis utilizes 4-hydroxy-2,3-dimethoxy-benzo-cycloheptan-6-one (i) as the starting material.



i

[14] H. Rapoport and J. E. Campion, *J. Amer. Chem. Soc.* **73**, 2239 (1951).

[15] A. Eschenmoser and H. H. Rennhard, *Helv. Chim. Acta* **36**, 290 (1953).

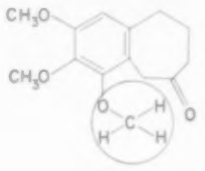
[16] In the experience of several groups (refs. 11 and 18, and others, by personal communication), the preparation of ketone III by the Eschenmoser procedure is handicapped by certain experimental difficulties. After several attempts, we were able to repeat the preparation; and subsequently, no further problems were encountered. The Rapoport approach was not tested in this Laboratory, but Prof. Rapoport informed one of us that the route, although comparatively long, is simply and reliably executed, thus allowing a quantity of the benzosuberone to be prepared with ease.

[17a] G. N. Walker, *J. Amer. Chem. Soc.* **77**, 6699 (1955); [b] T. A. Crabb and K. Schofield, *J. Chem. Soc.* 643 (1960).

[18] A. Eschenmoser, XVIth International Congress of Pure and Applied Chemistry, Division of Organic Chemistry, Paris, July 1957, *Congress Handbook* p. 272.

[19] G. Stork, R. Terrell and J. Szmuszkovicz, *J. Amer. Chem. Soc.* **76**, 2029 (1954).

bromoacetic ester—all without success. To our knowledge, the cyanoethylation reaction discussed in detail below represents the single successful alkylation operation so far observed for the trimethoxy-β-benzosuberone anion. Such difficulty was seemingly not encountered with the methoxy-free system, i.e. β-benzosuberone itself.[20] Since the electrical effect of the ether substituents should not be of over-riding importance in C-5 alkylation, the reluctance of ketone III to enter into such reactions must be



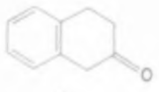
VIII

ascribed to direct steric interference in the 4-methoxyl group (VIII), an effect invoked in connection with other aspects[21] of colchicine chemistry.[22]

[20] W. J. Horton and G. Thompson, *J. Amer. Chem. Soc.* **76**, 1909 (1954).

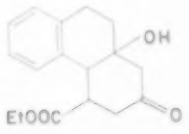
[21a] D. S. Tarbell, R. F. Smith and V. Boekelheide, *J. Amer. Chem. Soc.* **76**, 2470 (1954); [b] T. Nozoe, Y. Kitahara and S. Masamune, *Proc. Japan Acad.* **29**, 17 (1953), and preceding papers; [c] H. Rapoport and J. B. Lavigne, *J. Amer. Chem. Soc.* **78**, 2455 (1956).

[22] In connection with our attempts to utilize ketone III in simple alkylation and Michael-type reactions, a number of model experiments involving the more available β-tetralone (ii) were carried out in the early

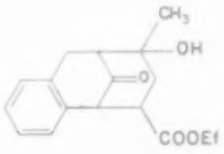


ii

stages of this work. From the reaction of β-tetralone and ethyl β-acetylacrylate in the presence of sodium methoxide, there was formed a *ketol*, m.p. 200–202·5° (dec.), of the expected composition (initial observation of E. Saito of this department). Chemical studies of this substance soon revealed behavior inconsistent with the structure normally anticipated (iii), and necessitated consideration of the alternative iv, formed by



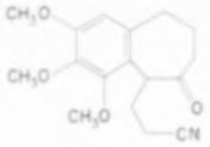
iii



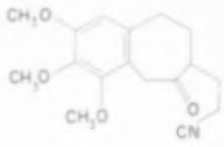
iv

initial Michael condensation at the expected site on the unsaturated ester, followed by attack of the hydroaromatic C-3 anion on the acyclic ketone function, leading to iv. The ketol exhibited infrared bands due to alcoholic hydroxyl and carbonyl functions; the ultraviolet spectrum showed the presence of only a simple benzenoid chromophore. All attempts to dehydrate the ketol, using either basic or acidic catalysts, to an α,β-unsaturated ketone were abortive. On being heated with ethyl orthoformate in the presence of sulfuric acid, the ketol was converted to a mixture of two isomeric *diethyl ketals of unsaturated ketoesters* (m.p.'s 112–113° and 88–89°). On the basis of ultraviolet and infrared spectral character (especially a newly-appearing medium band at 11·18 μ), the lower melting ketal was suspected of being the transformation product (v), and the isomer, then, the product (vi) resulting from the alternative mode of dehydration. In order to provide additional evidence for these conclusions, ozonization of the lower-melting ketal was carried out; as demanded by structure (v), formaldehyde was generated, in good yield. Consistent with

5(β-Cyanoethyl)-2,3,4-trimethoxy-benzocycloheptan-6-one (IX), m.p. 110–111°, was produced when the parent ketone III was exposed to the action of one or two



IX

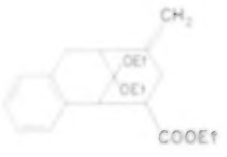


X

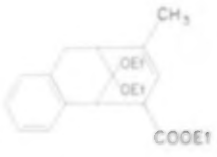
moles of acrylonitrile at room temperature for some hours in the presence of potassium t-butoxide. There seemed to be little doubt that in this case the normal reactivity

---

the β,γ-unsaturated formulation (vi), the higher-melting ketal was converted on treatment with methanolic sodium methoxide to a product (not isolated) which exhibited much enhanced ultraviolet absorption at 220 mμ (ε = 4600 → ε = 10,500), ascribed to the appearance of the isomeric α,β-unsaturated ester. Also, the nmr spectra of the ketol (as the O-acetate) and the methylene ketal were obtained, and were shown to be consistent with the assigned structures.



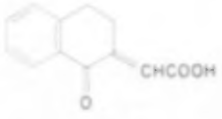
v



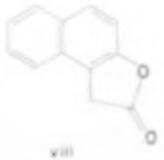
vi

In a more complete and definitive study, W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta [*J. Amer. Chem. Soc.* **82**, 614 (1960)] demonstrated the frequent formation of bridged ketols in the general Robinson annulation sequence.

In consideration of a particular approach to colchicine, reaction of β-tetralone, as a model, with glyoxylic acid or ester was envisioned. Although M. S. Newman and W. C. Sagar (personal communication) had found that α-tetralone was smoothly converted to the γ-keto-α,β-unsaturated acid (vii) on

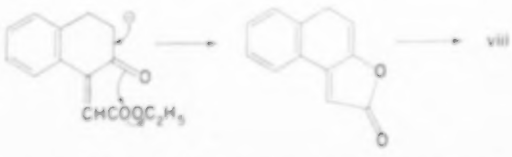


vii



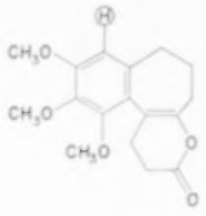
viii

treatment with the reagent in the presence of base, a similar experiment with the β-ketone failed. However, when ethyl glyoxylate was used instead, there was isolated in small yield the *lactone* (viii), undoubtedly

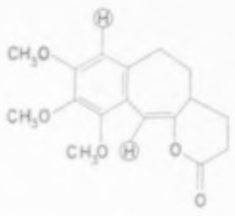


arising by initial formation of the unsaturated keto ester, followed by enol lactonization and isomerization of the double bonds. As stated earlier, no useful result was forthcoming on attempting similar reactions with trimethoxy-β-benzosuberone.

pattern of benzyl-type ketones would prevail, leading to bond formation at the 5-, and not the 7-position. This point of view is supported by the fact that, despite the presence of a significant excess of starting nitrile in the reaction medium, a mono-, and not a dicyanoethylated product was formed, surely a consequence of steric interference operative in the environment of the 5-, but not the 7-position.[23] Nevertheless, as a guard against the unexpected, effort was expended to establish rigorously the structure of the cyanoethylketone IX, the starting material for the synthesis. On successive treatment with methanolic potassium hydroxide and acetic anhydride–sodium acetate, the cyanoketone was converted through the keto acid to the enol lactone, m.p. 104–105°



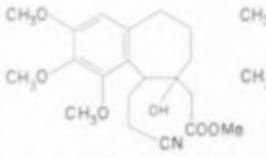
XI



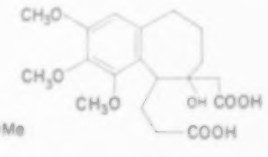
XII

(—CO—, 5·74 μ; C=C, 6·02 μ). Since, as evidenced by the ultraviolet absorption (λ_{max} 262 mμ, ε = 14,000), the new double bond was conjugated with the aromatic ring, only two structures were possible for the lactone: XI and the less likely XII. Formulation XI was unambiguously confirmed by its NMR behavior: in addition to the expected O-methyl and methylene proton resonances, a *single* peak corresponding to *one* hydrogen on an aromatic ring was found. Structure XII was thereby excluded, in that it would require an additional one proton band to appear in the olefinic hydrogen region.[24]

The cyanoketone contains two fewer carbon atoms than are present in the skeleton of colchicine itself. In the expectation that the construction of the alkaloid framework could be completed by using an acyloin reaction to close the third ring, we planned next to introduce an acetic acid side chain into the intermediate available at this point. When the cyanoketone was subjected to the action of zinc and methyl bromoacetate[25], there was formed in good yield a mixture of products, which was separated by a combination of chromatographic and crystallization techniques. Two of the



XIIIa–b



XIV

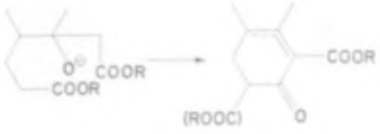
[23] On the other hand, the 7-anion, although not generated as often from this less acidic center, would be more basic, and therefore probably more nucleophilic; this factor, when coupled with the adverse steric effects known to prevail at C-5, might conceivably have led to preferential alkylation at C-7.

[24] The authors are indebted to Professor Paul Bender of this department, and Mr. Ronald J. Wingender for the determination of this NMR spectrum. Details of the NMR study may be found in the B.S. Thesis of R. J. Wingender, University of Wisconsin, 1958.

[25] W. E. Bachmann, W. Cole and A. L. Wilds, *J. Amer. Chem. Soc.* **62**, 824 (1940).

products formed were the *cis* and *trans* cyanohydroxyesters XIIIa (m.p. 119–119·5°) and XIIIb (m.p. 145–146°), the first being predominant. A third product, formed in variable amount, was identified as an ester lactone.[26] On saponification with refluxing methanolic potassium hydroxide, each of the cyanohydroxyesters was converted to the corresponding hydroxydiacid, the one (XIVa) derived from XIIIa melting at 83–88°, and the other (XIVb), at 206–208°.[27]

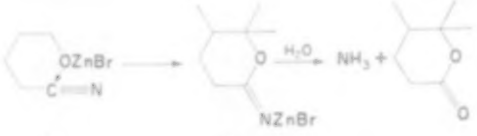
With the bicyclic diacids XIVa and XIVb available, an acyloin ring closure became a matter of practical interest; and there arose the question of which particular modification of the diacid would be most suitable for this operation. The simplest plan, that of using the diester of the hydroxydiacid itself, was dismissed at the beginning, since the free hydroxyl group portended serious difficulty in the step planned. Even if reversal to ring-B ketone or elimination to the α,β-unsaturated ester did not supervene, the readily formed tertiary alcoholic anion would very likely promote Dieckmann ring



XV

closure at the expense of acyloin formation. In fact, even under more nearly ideal conditions (see below), formation of a cyclic β-keto ester (XV) could not be entirely avoided. Preventing alkoxide formation by direct protection of the hydroxyl group was also considered and discarded, in that conversion of the tertiary function to derivatives appeared neither attractive nor expedient. A somewhat different solution was

[26] The side reaction leading to the lactone was capricious. Although the pathway followed is unexceptional (e.g. ix → x), the experimental factors controlling this ring closure were obscure and were not studied. Similar behavior in the Reformatsky reaction has been reported by R. D. H. Heard, G. A. Balla, J. R. Jamieson and P. Ziegler, *Canad. J. Chem.* **36**, 1260 (1958), and references cited therein.



ix x

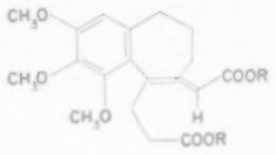
[27] Although base-promoted dehydration (1) or collapse to acetic ester and ketone (2) of a Reformatsky

(1)

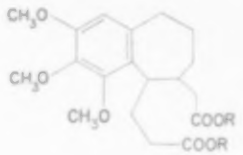
(2)

product can occur (see ref. 25), neither phenomenon was observed in the present case. Certainly the behavior of the β-hydroxy ester in situations of this kind is dictated largely by the rate of saponification relative to the rate of dehydration or reversal. All are virtually irreversible processes; and β-hydroxycarboxylic acid anion, once formed, is not prone to further change by process (1) or (2). In highly substituted cases, these latter two reactions become of importance because, first, each brings relief of steric compression, and also, rate of (1) and (2) becomes larger relative to that of saponification, which is decreased by reason of the same steric factors.

considered: deliberate dehydration to, and use of, the unsaturated diester. In this case, however, the geometry of the starting material might be unfavorable for ring closure, i.e. the ester groups might be *trans* (XVI) with respect to the double bond—in fact the more likely relationship in that hypothetical intermediate. Still another course of



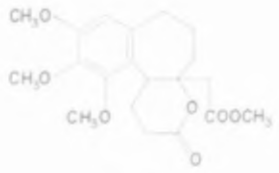
XVI



XVII

action was acyloin ring closure of the saturated diester (XVII). Almost certainly this substance could be obtained, and—notwithstanding failure in somewhat similar cases[28]—cyclization to the 1,2-ketol seemed reasonable. However, in this instance the ring-C which would be formed is saturated. In view of the probable sensitivity of ring-A to reagents useful for aromatization of hydrotropolones e.g. bromine or N-bromosuccinimide, retention of the oxidation state represented by the original hydroxydiacid XIV would be desirable, in that dehydrogenation should in that case be a simpler matter.

One method remained by which the troublesome tertiary oxygen function can be retained and protected, at the same time that the system is girded for ring-closure: reaction utilizing the lactone ester (XVIII).



XVIII

Limited by the above considerations to a particular variant of the acyloin reaction, we next inquire into the more detailed aspects of the chosen system (XVIII) which bear on the practicability of this all-important step. In regard to general formation of hexahydrotropolones from pimelic esters, the simplest case was described by Cram[29] some years ago, although it should be admitted that more complicated systems were reported later not to give the anticipated products, for reasons which seem not to be well understood. Although formation of cyclic acyloins by the action of sodium on a *lactone ester* had never been reported, there seemed to be in general no reason for discouragement from this direction.

However, a discrete reason for pause is given by the β-acyloxyester system included

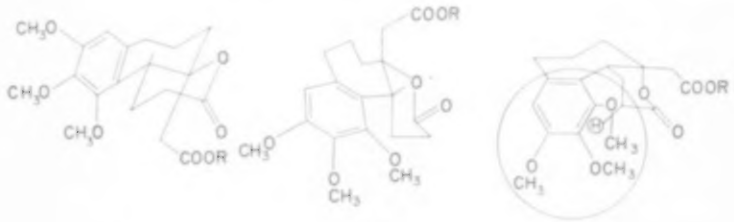
[28a] P. D. Gardner, G. R. Haynes and R. L. Brandon, *J. Org. Chem.* **22**, 1206 (1957); [b] N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.* **80**, 6630 (1958).
[29] J. D. Knight and D. J. Cram, *J. Amer. Chem. Soc.* **73**, 4139 (1951).

in structure XVIII. Since alkoxide anion is one of the products in the acyloin condensation, there arises the question whether this base could promote elimination to half acid ester (XIX), a development which would reduce considerably the yield of the desired tricarbocyclic product. Although a firm conclusion cannot be drawn, it seemed

XVIII XIX

possible that initial carbon–carbon bond formation in the acyloin reaction would proceed at a greater rate than release of alkoxide ion and/or elimination to XIX promoted by that base. Despite the fact that alkoxide appears as one of the products during acyloin formation, a reaction characteristically brought about by this reagent, *viz.* the acetoacetic ester condensation, is usually not observed during a normal acyloin operation,[30] not even in cases which would favor that side reaction (e.g. formation of a five- or six-membered cyclic β-keto ester). The implied ratio of reaction rates thus suggests that other alkoxide dependent processes, such as the elimination of XVIII to XIX, are not obligatory under the conditions of the acyloin reaction.

Conformational aspects of the proposed cyclization also should be examined. Although the three-dimensional relationships cannot be described exactly, the representations XX and XXI for the *trans* and *cis* fused isomers, respectively, are sufficiently



XX XXI XXII

accurate for present purposes. It is clear that the *trans* lactone ester is "frozen" in the conformation XX, whereas for the *cis* fused isomer, an alternative (XXII) is possible. In XXII, however, there is present a particularly severe steric interaction, the one involving ring-A and a ring-C axial hydrogen (both encircled), a factor rendering XXI the more likely expression for the normal state of the *cis* lactone. Now, in the initial phase of the acyloin reaction, it would appear that the two carbonyl groups (or their equivalents) approach each other within bond-forming distance while the ether oxygens remain intact. The process thus amounts to the incipient formation of a (3.2.1) bicycloöctane (XXIII), and, in conformance with all such cases, the atoms constituting the two-membered bridge must be axially bound to the bridgehead

[30] S. M. McElvain, *Organic Reactions* Vol. IV, p. 256. John Wiley, New York (1948).

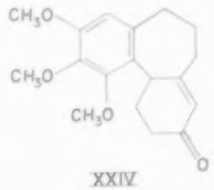
carbons of the second, six-membered ring. It is apparent that the *trans*-fused lactone

XXIII

ester is well-suited in this respect for acyloin formation, in that the acetic ester side chain is fixed in the required, axial position. The preferred conformation of the *cis* isomer (XXI) incorporates (in respect to the lactone ring) an equatorial acetic ester substituent, and in this state cannot cyclize; and if it is believed that conversion to the alternative XXII is infrequent, production of a ring ketol from the *cis* lactone seems unlikely.

In order to prepare for the selected stratagem, efforts were made to transform the hydroxydiacids XIVa and XIVb into the lactone esters. Formation of the required substances proved, however, to be troublesome. The hydroxy diesters were resistant to cyclization, as were the starting diacids, under normal ring closure conditions. As a consequence, we became dependent on the facility of N,N′-dicyclohexylcarbodiimide for dehydrations of this type.[31] Treatment of either hydroxydiacid with the aforementioned reagent, followed by esterification with diazomethane, provided the corresponding lactone ester, XVIIIa (m.p. 148–149°) or XVIIIb (m.p. 150–150·5°).[32]

Subsequent to the considerations and conclusions presented above, a variety of acyloin ring closures on both lactone esters were attempted. In general two techniques were employed: use of a sodium dispersion in an inert hydrocarbon medium, or sodium in liquid ammonia.[33] After each run, assay for the presence of an α-ketol grouping was carried out by means of a sodium metaperiodate titration. In no case was any sensible amount of periodate-oxidizable material produced from the more plentiful lactone ester XVIIIa. The action of sodium in liquid ammonia led to only a small amount of crystalline material, which appeared on the basis of its infrared spectrum to be a polyhydroxylic reduction product. Sodium in refluxing xylene converted lactone XVIIIa to a mixture, from which, by chromatography, two new substances were isolated. On the basis of analyses and spectral behavior, one of these was formulated as the cyclohexenone XXIV, arising through Dieckmann condensation,



XXIV

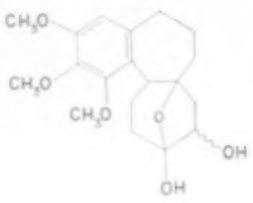
[31a] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.* **77**, 1067 (1955); [b] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

[32] Intermediate XVIIIa was identical with the lactone encountered in the Reformatsky reaction already discussed.

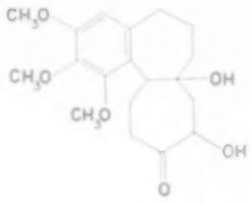
[33] J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.* **79**, 6050 (1957), and references cited therein.

dehydration and decarbomethoxylation. The second material, less well characterized, was tentatively regarded as the direct Dieckmann product, an unsaturated cyclic β-ketoester.

On being subjected to the action of sodium in xylene, the second lactone ester (XVIIIb) was converted to products which again failed to react with periodate and from which could be isolated only a small amount of ketone XXIV. Finally, when the sodium in liquid ammonia conditions were applied to the less available lactone ester, a wealth of new material was formed. On chromatography of non-acidic products,[34]

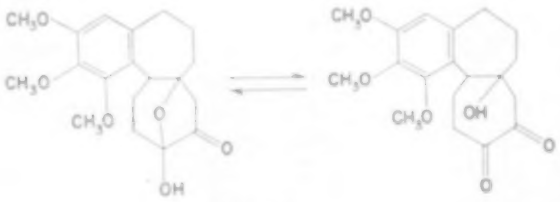


XXV



XXVI

three principal fractions (apart from starting lactone ester) were isolated, two of which consumed approximately an equivalent each of periodate, and were therefore concluded to be acyloins. Surprisingly, neither of the two oxidizable substances exhibited normal, strong carbonyl absorption in the infrared; however, intense hydroxyl bands were present. On the basis of these results, the two compounds were regarded as diastereoisomeric hemiketals (XXV) corresponding to the desired tricyclic structure XXVI, and in the case of the more plentiful isomer (m.p. 149–154°), this assignment was confirmed by further conversions. Thus acyloin ring closure had been achieved with, moreover, retention of the *t*-hydroxyl function.



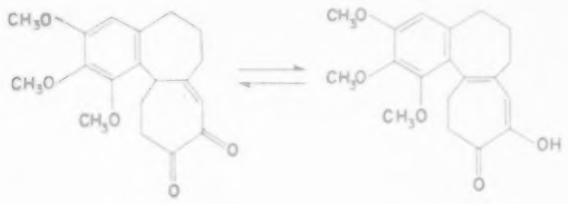
XXVII

In view of earlier considerations and only on the basis of the results of the acyloin reaction experiments, lactone XVIIIa is assigned the stereochemistry XXI (*cis*), while the isomer XVIIIb is to be regarded as the *trans*-fused type (XX).

With this major hurdle safely negotiated, we proceeded with the next leg in the synthetic pathway, conversion of the tetracyclic hemiketal (XXV) to desacetamidocolchiceine. Because selectivity in the dehydrogenation would be advisable, if not

[34] The major constituent of acidic material isolated was hydroxydiacid XIVb. In one run, in which the product was subjected to the action of cupric acetate, a substance $C_{28}H_{28}O_7$, presumed to be unsaturated diacid, was isolated.

mandatory, the masked acyloin was oxidized first to the corresponding ketone XXVII (m.p. 203–204·5°), using cupric acetate in methanol.[33] In agreement with the presence of a strained five-membered ring ketone moiety in the assigned structure, a carbonyl band at 5·68 μ was located in the infrared. Despite the fact that the intermediate available at this stage was a dihydrotropolone, and ready conversion to the aromatic system might be anticipated, neither N-bromosuccinimide nor molecular bromide[35] produced any detectable amount of tropolonoid product. Special stability is inherent in the bridged system of XXVII, and stepwise conversion to desacetamidocolchiceine was indicated. Alkoxide-catalyzed dehydration was unsuccessful; but it was found that *p*-toluenesulfonic acid in refluxing benzene served to dehydrate the hemiketal along desired lines. As indicated by ultraviolet spectral behavior, the resulting α,β-unsaturated diketone (XXVIIIa) exists principally as the enol XXVIIIb. The simplest version of aromatization is now possible; and indeed, the crude enedione, on being heated briefly with one equivalent of N-bromosuccinimide in chloroform, was easily



XXVIIIa XXVIIIb

transformed to desacetamidocolchiceine (V). Comparison with material of similar structure secured by degradation of colchicine (see next section) showed the two substances to be identical.

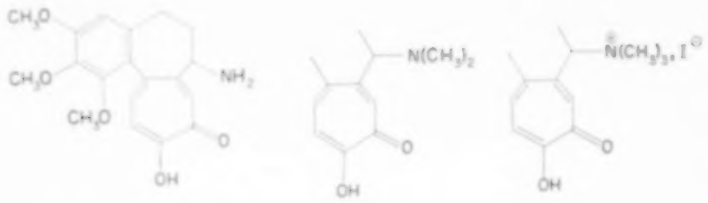
INTERCONVERSION OF COLCHICINE AND DESACETAMIDOCOLCHICEINE

In regard to the second phase of the synthetic program, the transformation of desacetamidocolchiceine to colchicine, it had always been evident that the required steps could best be managed as a relay operation. Accordingly, while progress was being made in the first phase of the work, we began experiments designed to remove selectively nitrogen from the naturally-occurring system, with the ultimate purpose of using the desacetamidocolchiceine so produced for the completion of the remaining steps in the total synthesis.

Although deamination in the colchicine series had been reported by previous workers, the process was carried out only in cases involving a rearranged skeleton.[36] Thus the immediate problem was the design of some procedure by which nitrogen might be removed, but without effect on the tropolone, or any other, portion of the

[33] T. Nozoe, S. Seto, Y. Kitahara, M. Kunori and Y. Yakahama, *Proc. Japan Acad.* **26**, 38 (1950).
[36] See J. W. Cook and J. D. Loudon in R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. II, p. 261. Academic Press, New York (1959).

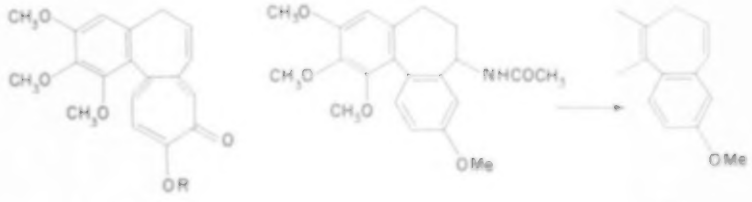
molecule.[37] If ring-C is looked upon as aromatic, then nitrogen is in a benzylic position; and direct hydrogenolytic removal of that atom should be possible, as is the case with more orthodox benzyl type amines.



XXIX XXX XXXI

In preparation for the proposed reduction, trimethylcolchicinic acid (XXIX), made as previously described by direct acid-catalyzed hydrolysis of colchicine,[38] was

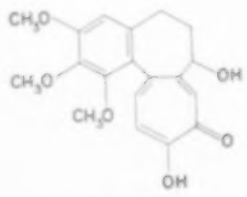
[37] Several methods for nitrogen removal—other than most successful, described above—were investigated in this Laboratory. Of those which gave recognizable results, there may be mentioned first the attempted elimination to olefin (xi) by means of phosphorus pentoxide, patterned after the recorded conversion of



xi xii xiii

xii to xiii [J. W. Cook, W. Graham, A. Cohen, R. W. Lapsley and C. A. Lawrence, *J. Chem. Soc.* 322 (1944)]. In the colchicine case, either starting material was recovered or seriously degraded under the various conditions applied. It seems likely that the basic nature of the tropolone ring protects the adjacent ring-B carbon from alteration by acids, i.e. the presence of a substituted tropolone as the conjugate acid may render carbonium ion formation at the benzylic position more difficult.

The action of nitrous acid on trimethylcolchicinic acid was devastating, but extensive chromatography of the dark, resinous product allowed isolation of a small yield of crystalline product, m.p. 181–183°. Elemental, infrared and ultraviolet spectral analyses suggested the presence of intact rings A and C, as well as an alcoholic hydroxyl group. Barring rearrangement of ring B, the assignment of structure xiv to this product may be made.



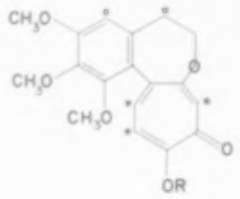
xiv

[38] J. N. Ashley and J. O. Harris, *J. Chem. Soc.* 677 (1944).

subjected to N-methylation conditions. Prolonged heating of the starting base with excess methyl iodide in dioxane brought the alkylation to the N,N-dimethyl stage, the hydroiodide of the tertiary base (XXX) crystallizing out of the reaction medium as the reaction proceeded.[39] Preparation of the quaternary salt (XXXI) by direct permethylation of trimethylcolchicinic acid was not satisfactory, and therefore XXXI (m.p. 232–235·5°) was prepared by subjecting the free tertiary amine to the same conditions used for the initial N-methylation.

Only one method—but an eminently suitable one—for reductive deamination of the quaternary salt was investigated, catalytic (Pd-on-C) hydrogenolysis carried out in aqueous sodium hydroxide at room temperature.[40,41] As a result of this treatment there was produced directly desacetamidocolchiceine, identical (as indicated before) with the material obtained by the purely synthetic route. The overall preparation from colchicine is readily executed, and by its means adequate amounts of desacetamidocolchiceine were made available for the relay reactions described below.

The proposed conversion of desacetamidocolchiceine to colchicine is by and large a matter of selectivity, although a variety of reagents which might be suitable for functionalizing at the necessary site came under consideration. If the C-ring is broadly considered as an aromatic unit, it would appear that activation of the carbon atom

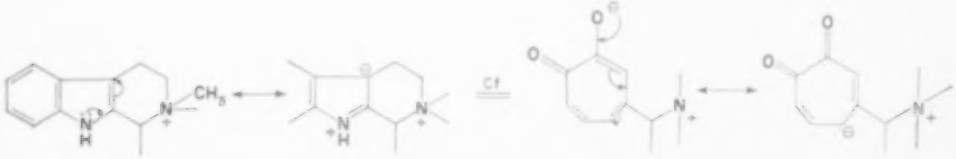


XXXII

which requires modification (encircled, XXXII) might be possible by means of carbonium ion, carbanion or free radical formation. Introduction of oxygen or halogen (or nitrogen) in the functionalization step was regarded as acceptable, since replacement of

[39] Dimethylation, under other conditions, of trimethylcolchicinic acid was first reported by V. V. Kiselev and G. P. Men'shikov, *Dokl. Akad. Nauk SSSR* **88**, 825 (1953).

[40] An interesting parallel after which our procedure was patterned, is a reduction carried out in the mavacurine series by K. Bernauer, H. Schmid and P. Karrer, *Helv. Chim. Acta* **40**, 731 (1957).

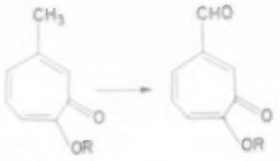


[41] Inorganic base is not uncommonly employed during catalytic reductions of this type. In the case of XXXI, the alkali probably provides the important service of preventing reduction of ring-C during the hydrogenolysis; the anion is more stable than the parent acid, and therefore reduction of the tropolone ring should be more difficult. Experimentally, the hydrogen uptake of XXXI in the presence of alkali ceased after one mole; however, attack of a tropolone as the *free acid* using the same catalyst is recorded,[12] and was also observed in this Laboratory.

Hydrogenolysis of trimethylcolchicinic acid itself or N,N-dimethylcolchicinic acid was not successful.

either with nitrogen should be no serious problem. On the other hand, many of the reagents considered were likely to affect other vulnerable spots in the tricyclic system, in general those indicated by asterisks in formula XXXII.

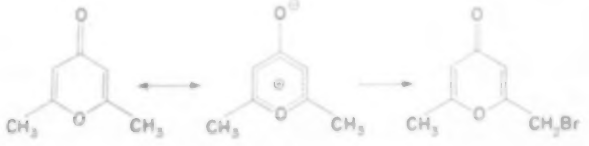
Of the various schemes considered, one which appeared particularly promising was oxidation to the benzylic alcohol, or the corresponding ketone, by means of selenium dioxide. A fortuitously close analogy was available in the work of Haworth and Hobson[42], who oxidized β-methyltropolone (XXXIII) (or its methyl ether) by means



XXXIII

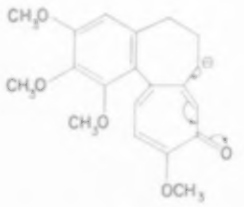
of this reagent to the tropolone aldehyde; saturated carbon *gamma* to, and therefore vinylogously activated by, a carbonyl group is a common feature of structures XXXII and XXXIII. Unfortunately, desacetamidocolchiceine as well as the isomeric ring-C methyl ethers were very resistant to the action of selenium dioxide, and in an extreme case, one of the ethers was recovered in good measure after being refluxed for some hours with the reagent in cyclohexanol.[43]

N-bromosuccinimide is commonly used for side chain bromination of alkyl substituted aromatic systems, and consequently this agent offered hope in the present



[42] R. D. Haworth and J. D. Hobson, *J. Chem. Soc.* 561 (1951).

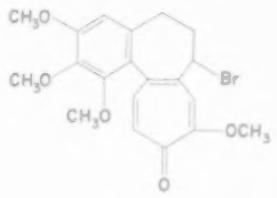
[43] Other attempts to oxidize desacetamidocolchiceine methyl ether in the desired fashion were made. Among these were the reactions with lead tetraacetate in glacial acetic acid, t-butyl hydroperoxide with a heavy metal catalyst in t-butanol or acetic acid, and chromium trioxide in acetic acid. In all cases, in addition to starting material, there was isolated product in which the tropolone ring was no longer intact (by I.R. and U.V.). In a single attempt to generate and use the anion XV, one of the ring-C ethers was treated successively with sodium triphenylmethyl and isoamyl nitrite in dioxane; again, no useful product resulted.



XV

circumstance. The question of whether side chain halogenation might be possible in *non-benzenoid* aromatic cases had been answered in the affirmative, e.g. in that 2,6-dimethyl-γ-pyrone was smoothly converted to the primary monobromide on treatment with the brominating agent.[44] The analogy to the tropolone case is strikingly close. Moreover, the rate of the pyrone bromination seems to be greater than that of *nuclear* bromination of methoxyl-substituted benzenes,[45] suggesting that ring-B halogenation of desacetamidocolchiceine might be achieved without concurrent halogenation of the A- and C-rings. Encouraged by these considerations, we initiated experiments along these lines. Shortly thereafter, we learned from Dr. Eschenmoser that the desired selective bromination had been recently executed within his group,[10] and we are indebted to him for providing us with information which facilitated our own endeavors in this direction.

The complication of nuclear ring-C halogenation is best avoided by using tropolone methyl ether as the substrate. As expected, treatment of desacetamidocolchiceine with diazomethane afforded a mixture of the two possible methyl ethers, which was used as such in connection with some of the experiments described in this section. For satisfactory results in the bromination step, however, an entity was highly desirable; and therefore the mixture of ethers was separated by fractional crystallization,[46] providing substances of m.p.s 149–150° and 183–184°. In agreement with the findings of Eschenmoser, reaction of the lower-melting ether with N-bromosuccinimide under normal conditions, led to generation of the substitution product XXXIV (m.p. 166–172°), containing a reactive halogen, in addition to a substance (m.p. 218–222° dec.)



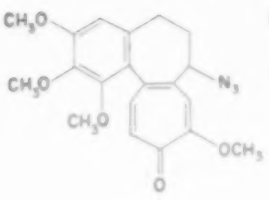
XXXIV

with inert—presumably aromatic—bromine. That the former substance possessed the assigned structure was proved—both in this Laboratory and at E.T.H.—by its conversion to colchicine.

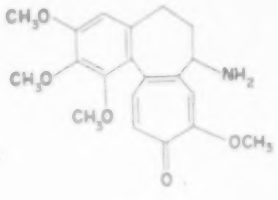
Introduction of nitrogen into the tricyclic intermediate XXXIV by displacement of bromine calls for, ideally, an anionic species in which basic character is outweighed by nucleophilic ability; in such a case, the undesirable elimination reaction to olefin can be suppressed, while the displacement to give substituted product is emphasized. These requirements are met well by *azide* ion, which characteristically acts to give a good yield of inversion product with various halides.[47] When the bromo compound XXXIV was heated for about a day with an excess of sodium azide in methanol at 90–95°, there was generated in good yield the alkyl azide XXXV (infrared band 4·72 μ).

[44] Ng. Ph. Buu-Hoï and J. Lecocq, *C.R. Acad. Sci., Paris* **222**, 1441 (1946).
[45] L. Horner and E. H. Winkelmann, *Angew. Chem.* **71**, 349 (1959).
[46] Chromatographic separation of the ethers, used by Dr. Eschenmoser, failed in our hands. The structure and reactivity aspects of the ethers are being presented elsewhere by Dr. Eschenmoser.
[47] For example, see H. Hellman, J. Lingens and E. Folz, *Chem. Ber.* **89**, 2433 (1956); A. Streitwieser, Jr. and W. D. Schaeffer, *J. Amer. Chem. Soc.* **79**, 2888 (1957).

Using arbitrarily chosen experimental conditions,[48] the azide intermediate was reduced with hydrogen in the presence of palladium-on-carbon to the corresponding primary amine (XXXVI), which was not purified but hydrolyzed directly with aqueous acid to



XXXV



XXXVI

the free tropolone, *dl*-trimethylcolchicinic acid (XXIX). Subsequent to chromatography on silicic acid and recrystallization from absolute ethanol, the end-product melted at 240–244° (dec). Comparison by means of melting point, mixed melting point, ultraviolet and infrared spectra showed the synthetic *dl*-trimethylcolchicinic acid to be identical with that prepared from natural colchicine according to the method of Corrodi and Hardegger.[49]

In view of the previously accomplished resolution of *dl*-trimethylcolchicinic acid (derived from the natural source) and its reconversion to colchicine,[49] the conversion of desacetamidocolchiceine to *dl*-trimethylcolchicinic acid marked the successful culmination of the present investigation, the last in the series of steps which constitute to total synthesis of colchicine.

EXPERIMENTAL

All melting points of analytical samples were taken in open capillary tubes in a Hershberg apparatus using Anschütz total immersion calibrated thermometers. All other melting points were taken on a hot stage and are approximately corrected for stem exposure. Boiling points are uncorrected.

Analyses were performed by the Microanalytical Laboratory of the University of Wisconsin, by the Huffman Microanalytical Laboratories, Wheatridge, Colorado, or by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Infrared spectra were taken in chloroform solution on a Baird Double-beam Self-recording Spectrophotometer unless otherwise specified. Ultraviolet spectra were taken in 95% ethanol solution on a Cary Recording Spectrophotometer (Model 11 MS) unless otherwise specified.

NMR spectra were determined at 40 megacycles/second with a Varian Associates V-4300-B High Resolution NMR Spectrometer with associated 12″ magnet system equipped with a V-K3506 flux stabilizer. Deuterochloroform was employed as the solvent. Benzene or water, contained in a small internal capillary, was employed for reference. Chemical shifts are reported in cps (estimated accuracy ±2 cps) relative to benzene or water, as indicated. Audiofrequency side bands for calibration were generated and measured with a Hewlett-Packard 200-CD Audio Oscillator and 521-C Frequency Counter.

The chromatographic adsorbents which were used are designated in this section by the following names:

Alumina refers to Merck and Co. acid-washed aluminum oxide, Reagent Grade.

Florisil refers to the product of the Floridin Company, Tallahassee, Florida, 60/100 mesh.

Silicic acid refers to Mallinckrodt Analytical Reagent silicic acid which had been washed with acetone and oven-dried. *Silica gel* refers to the product as supplied by Mallinckrodt.

All solvents used for chromatography, reaction mixtures, or recrystallizations were reagent grade

[48] Because of the stoichiometry of the reduction,

$$R{-}N_3 + H_2 \rightarrow RNH_2 + N_2$$

there is no overall pressure change in the catalytic reduction of an azide to the primary amine.

[49] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **40**, 194 (1957).

solvents, used without further purification unless otherwise specified, with the exception of benzene, acetone and petroleum ether. These latter three were distilled prior to use. "Petroleum ether" refers throughout this section to material distilling in the range 66–68°.

All compounds referred to in this section are racemic unless otherwise specified. The prefix "*dl*" has been omitted, except in the case of trimethylcolchicinic acid, where it is retained to prevent confusion with the natural (—) material.

2-Hydroxy-2-methyl-4-carboethoxy-6,7-benzo-9-ketobicyclo (3.3.1.) *nonane*. To a solution of 1·0 g (0·004 mole) of sodium in 300 ml of anhydrous methanol, cooled in an ice bath and stirred magnetically, was added 5·0 g (0·034 mole) of β-tetralone (b.p. 130–135° at 10–12 mm). Then 4·8 g (0·034 mole) of ethyl β-acetylacrylate (b.p. 80–90° at 7 mm, n_D^{20} 1·4506) was added dropwise over a 5 min period. The mixture was stirred at room temperature for 40 min, during which time a small amount of white precipitate separated from the dark blue solution. The addition of 600 ml of water caused a large increase in the amount of precipitate. After 30 min the mixture was filtered, yielding 6·10 g (62·5%), m.p. 190–195°. Acidification of the filtrate and extraction with ether afforded only oily material which could not be induced to crystallize.

The product was purified by recrystallization from methanol four times to yield 4·74 g (48·5%) of large colorless cubes, m.p. 200–202·5° (dec.), λ_{max}^{KBr} 2·95 μ (OH), 5·75, 5·85 (C=O), λ_{max} 266 mμ (ε = 500). Gas was evolved during fusion of this compound and the melting point varied with the rate of heating.

(Found: C, 70·92; H, 6·90. $C_{17}H_{20}O_4$ requires: C, 70·81; H, 6·99).

From the mother liquors of one of the above preparations a few milligrams of a compound, m.p. 163–165°, was isolated. The similarity of its infrared and ultraviolet spectra to those of the ketol suggested that it might be the C-2 epimer of that compound.

The bridged ketol was also obtained using the Stork enamine alkylation method. The pyrrolidine enamine of β-tetralone, m.p. 81–82°, was prepared by heating β-tetralone with an excess of purified pyrrolidine, b.p. 86·5–87·0°, in benzene solution for 3 hr attached to a Dean-Stark water separator.

One gram (0·005 mole) of purified enamine, m.p. 81–82°, and 0·72 g (0·0051 mole) of ethyl β-acetylacrylate (b.p. 80–90° at 7 mm) were dissolved in 25 ml of anhydrous benzene and stirred for 14 hr at room temperature. Most of the benzene was removed by distillation at reduced pressure. A solution of 5 ml of glacial acetic acid, 5 ml of water, and 1 g of sodium acetate in 50 ml of methanol was added and the resulting mixture was heated at reflux to effect hydrolysis of enamine products. Most of the methanol was removed by distillation at reduced pressure and 50 ml of water was added to the dark green solution causing separation of a dark, tarry viscous oil. From this residue a small amount of crystalline material was obtained by trituration with absolute ethanol. Recrystallization of this material from methanol afforded a small yield of the familiar ketol, m.p. 200–202·5° (dec.). No chromatographic investigation of the remainder of the tarry product was made.

The reaction of ketol with ethyl orthoformate. To 1·00 g (0·00348 mole) of pulverized ketol, m.p. 200–202·5° (dec.), suspended in 5 ml anhydrous ethanol was added 3 ml of freshly distilled ethyl orthoformate, b.p. 144–145°, and one drop of concentrated sulfuric acid. The mixture was heated at 60° for 3 hr, with swirling to aid in the initial dissolving of the solid ketol.

The solution was cooled and treated with excess solid sodium carbonate. After the mixture became neutral (pH paper), the yellow solution was filtered from the sodium carbonate, which was washed with ethanol, and the combined organic layers were evaporated. Trituration of the residue with methanol induced slow crystallization to a mixture of oily solids weighing 0·55 g. From this crystalline mixture could be isolated small amounts of the two dehydrated ketals. For preparation of these individual compounds it was found desirable to modify the reaction conditions in order to obtain one or the other in preponderant amount.

2-Methylene-4-carboethoxy-6,7-benzo-9,9-diethoxybicyclo [3.3.1] nonane, could be made the major product (10–20% yield, pure) if the reaction were run at 80° for 10 min. Recrystallization of the product from such conditions from methanol afforded colorless plates, m.p. 87·6–88·7°, λ_{max} 5·85 μ, 6·12 (weak), 11·18 (medium); NMR, peak at 65 cps relative to benzene (=CH_2).

(Found: C, 73·18; H, 8·11. $C_{21}H_{28}O_4$ requires: C, 73·23; H, 8·19).

If the isomeric ketal, 2-methyl-4-carboethoxy-6,7-benzo-9,9-diethoxybicyclo [3.3.1] nonene-2, was the desired product, the reaction was run at 60° for 6 hr. From such a reaction product, by recrystallization from methanol-water, a 10–25% yield of colorless rods, m.p. 111·6–112·8°, λ_{max} 5·85 μ (C=O) could be isolated.

(Found: C, 72·92; H, 7·83. $C_{21}H_{28}O_4$ requires: C, 73·23; H, 8·19).

Attempts to convert both ketals to the corresponding ketones by means of acid hydrolysis failed to yield any crystalline products.

Ozonolysis of 2-methylene-4-carboethoxy-6,7-benzo-9,9-diethoxybicyclo [3.3.1] *nonane*. A solution of 90·6 mg ($2·64 \times 10^{-4}$ mole) of the exocyclic methylene ketal, m.p. 85–87°, in 10 ml of glacial acetic acid was treated with an excess of ozonized oxygen (generated by a Wellsbach Model T-23 ozonizer) for 40 min at room temperature. The resulting mixture was immediately steam-distilled until approximately 350 ml of distillate had been collected in an ice-cooled flask.

About half-way through the distillation a solution of 148 mg ($1·05 \times 10^{-3}$ mole) of dimedone in 5 ml of ethnaol was added to the distillate. At the end of the steam-distillation period the mixture was brought to a pH of 4·5 (as indicated by pH paper) by addition of dilute sodium hydroxide solution and set in the refrigerator overnight, whereupon a precipitate of silky needles separated. After collecting and vacuum-drying, this crude dimedone dreivative of formaldehyde weighed 52·2 mg (67·7%), m.p. 165–189°. Recrystallization from dilute ethanol afforded 34·4 mg. (44·7%) of silky needles, m.p. 187·5–189·5°. Upon admixture with an authentic sample of formaldehyde methone, m.p. 189·5–191°, the melting point was 188·5–191°.

Treatment of 2-methyl-4-carboethoxy-6,7-benzo-9,9-diethoxybicyclo [3.3.1] *nonene-2 with base*. Sodium methoxide solution was employed to try to obtain spectral evidence for base-catalyzed shift of the 2,3 double bond into conjugation with the carboethoxy group. The ketal, m.p. 111·6–112·8°, had absorption in its ultraviolet spectrum at 220 mμ of intensity $\varepsilon = 4600$ in anhydrous methanol solution. To a solution of 0·23 g (0·01 mole) of sodium in 100 ml of anhydrous methanol was added 5·1 mg. ($1·48 \times 10^{-5}$ mole) of ketal and the mixture was allowed to stand at room temperature for 2 hr. At the end of this time the intensity of the absorption at 220 mμ had increased to $\varepsilon = 10{,}500$.

2-Acetoxy-2-methyl-4-carboethoxy-6,7-benzo-9-ketobicyclo-[3.3.1] *nonane*. The bridged ketol, 1·0 g (0·0035 mole), m.p. 200–202·5° (dec.), and two drops of concentrated sulfuric acid were added to 25 ml of distilled isopropenyl acetate, b.p. 95–96°, and the mixture was refluxed until it became homogeneous. The yellow solution was evaporated to dryness under reduced pressure, affording a partially crystalline residue. Recrystallization from methanol gave about 0·3 g (26%) of large colorless needles, m.p. 126–129°. An analytical sample, prepared by recrystallization from methanol, exhibited dimorphism, partially melting at 126·5°, resolidifying, and then melting at 129·0–130·0°; λ_{max} 5·85 μ,

no hydroxyl band; NMR, peaks 167 cps (—C—CH_3), 177 cps (—C—CH_3), 193 cps (—CH_2CH_3) relative to benzene.

(Found: C, 69·34; H, 6·56. $C_{19}H_{22}O_5$ requires: C, 69·07; H, 6·71.)

Reaction of β-tetralone with ethyl glyoxylate. To a solution of 0·10 g (0·00435 mole) of sodium in 40 ml of absolute ethanol were added 3·0 g (0·0205 mole) of β-tetralone, b.p. 130–135° at 10–12 mm, and 4·5 g (0·0305 mole) of the alcoholate of ethyl glyoxylate, b.p. 134·5–136·0°, and the mixture was refluxed for 16 hr attached to a Dean-Stark water separator. Acidification with dilute hydrochloric acid, followed by ether extraction, afforded 4·05 g of wine-red oil, which did not crystallize and was accordingly chromatographed on 100 g of Florisil using a petroleum ether–benzene-ether eluent sequence. Elution with benzene afforded fractions containing white crystals, m.p. 92–100°, in about 10% yield. Purification of this material by recrystallization proved difficult, but it readily sublimed at 70–75° at 0·1 mm to give white needles, m.p. 104–105°, λ_{max} 5·58 μ, λ_{max} 230 mμ ($\varepsilon = 60{,}000$), 270, 281, 294, 316, 323, 331 (two triplets, ε about 3000). These properties, particularly the strikingly characteristic β-naphthol ultraviolet spectral pattern, served to identify this product as 2-naphthol-1-acetic acid lactone.

This assignment was confirmed by comparison with an authentic specimen, m.p. 104–105°, prepared by the method of Mayer *et al.*[50], starting from 2-methoxy-1-naphthaldehyde. The infrared spectra of the two samples were identical and the melting point upon admixture was undepressed.

No other crystalline material was obtained from the chromatogram of the β-tetralone and ethyl glyoxylate reaction product.

2,3,4,-Trimethoxybenzo-5-cyanoethylcycloheptan-6-one (IX). To 10 ml of anhydrous tertiary butanol, distilled from calcium hydride, b.p. 82–83°, was added 94 mg (0·0024 mole) of freshly cut potassium under a stream of nitrogen. After the potassium was completely dissolved with the aid of

[50] F. Mayer, W. Schäfer and J. Rosenbach, *Arch. Pharm.* **267**, 571 (1929).

magnetic stirring and steam-bath heat, a solution of 599 mg (0·00239 mole) of 2,3,4-trimethoxybenzocycloheptan-6-one, m.p. 53–54°, in 10 ml of anhydrous tertiary butanol was added. To the light yellow anionic mixture a solution of 160 mg (0·00302 mole) of freshly distilled acrylonitrile, b.p. 76·5°, in 5 ml of anhydrous tertiary butanol was added dropwise over a 15 min period. The reaction mixture was allowed to stand at room termperature for 9 hr in the nitrogen atmosphere. A slight excess of glacial acetic acid was then added to the mixture, which became colorless upon neutralization. The solution was diluted with water and extracted thoroughly with chloroform. The organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to yield 753 mg (theoretical yield 725 mg) of an oil which readily crystallized upon trituration with ether. Recrystallization from ether (or, better, methanol) yielded 525 mg (72·5%), m.p. 108–110°. Further recrystallization afforded large prisms, m.p. 110·5–111·2°, λ_{max} 4·45 μ (C≡N), 5·90 μ (C=O).

(Found: C, 67·34; H, 6·93; N, 4·60. $C_{17}H_{21}O_4N$ requires: C, 6 7·31; H, 6·98; N, 4·62.)

By chromatography on alumina, using an acetone–petroleum ether eluent pair, further crystalline material could be obtained from combined mother liquors. Large-scale preparations of this cyanoethylation product were run on the crude product obtained from tetramethylpurpurogallin by sequential lithium aluminum hydride, zinc and sulfuric acid, and catalytic reductions. In these cases it was always necessary to chromatograph the entire product. The overall yield of cyanoketone from tetramethylpurpurogallin never exceeded 25% of the theoretical amount.

2,3,4-*Trimethoxybenzocyclohept-5-en-6-ol-5-propionic acid δ-lactone* (XI). The cyanoketone, 395 mg (0·00130 mole), m.p. 110–111°, was hydrolyzed to the corresponding ketoacid by refluxing it with 6 g of potassium hydroxide in 12 ml of methanol and 24 ml of water for 24 hr. Neutral material was removed by ether extraction of the basic aqueous mixture. Then the solution was acidified with dilute hydrochloric acid and extracted with ether. The organic extracts were dried over magnesium sulfate, filtered, and evaporated to yield 407 mg (98%) of crude acidic product which was used directly in the next step.

For conversion of the ketoacid to the enol-lactone, the 407 mg of product from the above hydrolysis dissolved in 20 ml of distilled acetic anhydride, b.p. 136–137°, 20 mg of sodium acetate was added; and the mixture was heated at 100° for 9 hr in an atmosphere of purified nitrogen. The acetic anhydride was removed by distillation at 80° under reduced pressure using a purified nitrogen capillary bleed. The residue was taken up in ether and the ether solution was washed twice with 5% sodium bicarbonate solution, once with water, dried over sodium sulfate, filtered, and evaporated to yield 264 mg (66·6% from cyanoketone) of crystalline material, m.p. 99–103°.

In order to remove traces of color from this product, it was dissolved in 5% acetone in petroleum ether and filtered through a column of 3·0 g of Florisil. Recrystallization of eluted material from petroleum ether afforded 221 mg (55·8%), m.p. 103·3–104·6°. Five further recrystallizations from petroleum ether gave an analytical sample, m.p. 104·0–105·2°, λ_{max} 262 mμ (ε = 14,000), λ_{max} 5·74 μ (strong), 6·02 (weak), NMR, peaks at −75 cps (vinyl H), +36 (OCH_3), 80, 101 (CH_2), relative to water.

Found: C, 66·80; H, 6·68. $C_{17}H_{20}O_5$ requires: C, 67·09; H, 6·62).

Another crystalline form of this enol-lactone, m.p. 89–90·5°, could be isolated from petroleum ether solution by rapid crystallization at refrigerator temperatures. By appropriate seeding of a hot petroleum ether solution of the compound either crystalline modification could be obtained.

One attempt to prepare this enol-lactone by treatment of the crude ketoacid with N,N′-dicyclohexylcarbodiimide in pyridine solution afforded none of the desired product, yielding instead a substance, m.p. 123–125°, which was tentatively assigned the structure of an N-acyl urea on the basis of its infrared spectrum, λ_{max} 3·0 μ (N—H), 5·9 μ (C=O), 6·05–6·1 μ (C—N).

Reformatsky reaction of 2,3,4-*trimethoxybenzo-5-cyanoethylcycloheptan-6-one*. The procedure used was based on that of Bachmann, Cole and Wilds[25]. The zinc (20 mesh) to be used was activated by washing with dilute hydrochloric acid, water, and acetone, and was dried briefly in the oven.

In a 1 l., three-necked, flame-dried flask equipped with a Teflon paddle stirrer and reflux condenser was placed a solution of 16·558 g (0·0547 mole) of the cyanoketone, m.p. 110–111°, in 75 ml of anhydrous benzene. To this was added 75 ml of anhydrous ether, approximately 25 g of the activated zinc, a few crystals of iodine, and approximately one-third of 34·0 g (0·222 mole) of methyl bromoacetate (freshly distilled, b.p. 143°). The mixture was stirred and heated gently at reflux. After about 15 min

the red iodine color disappeared and the solution became cloudy, indicating that the reaction had been initiated. Additions of the activated zinc were made often during the course of the reaction—a total of about 200 g being used. A few crystals of iodine (which decolorized immediately) and the remainder of the methyl bromoacetate, in three or four large portions, were added over a 90 min period. After about an hour the stirrer paddle became clogged with precipitate and agglutinated zinc and had to be stopped. The mixture was refluxed for a total of 3 hr, however.

At the end of this time, the precipitated complex was dissolved by adding excess acetic acid and a little methanol to the reaction flask. The solution was decanted from the residue of metallic zinc and extracted with water. The water layer was in turn extracted thoroughly with benzene. The combined organic layers were stripped of the volatile solvents by distillation under reduced pressure. Azeotropic distillation with toluene was used to remove excess acetic acid. The residue crystallized, but was chromatographed on 350 g of Alumina without any further purification, using an acetone–petroleum ether eluent pair.

Although the two diastereoisomeric cyanohydroxyesters were not completely separated by chromatography, careful elution with 10% acetone in petroleum ether afforded two maxima corresponding to greatest relative concentrations of compounds XIIIa and XIIIb. Fractions close to each maximum could be crystallized to yield their major component. However, extensive, laborious fractional crystallization of all material which could be induced to crystallize by trituration with ether was necessary to isolate any considerable yield of pure products. By these methods the reaction described above afforded 3·861 g (18·8%) of 2,3,4-trimethoxybenzo-5-cyanoethyl-6-carbomethoxymethylcycloheptan-6-ol (XIIIb), m.p. 142–145°. Recrystallization from acetone-petroleum ether afforded colorless needles, m.p. 145·0–145·8°, λ_{max} 2·85 μ (OH), 4·45 (C≡N), 5·85 (C=O).

(Found: C, 63·54; H, 7·39; N, 3·8. $C_{20}H_{27}O_8N$ requires: C, 63·64; H, 7·21; N, 3·71).

The major product from the Reformatsky reaction, 2,3,4-trimethoxy-5-cyanoethyl-6-carbomethoxymethylcycloheptan-6-ol (XIIIa), amounted to 7·744 g (37.6%) of large clusters of colorless prisms, m.p. 118–120°. Recrystallization from acetone-petroleum ether afforded an analytical sample, m.p. 118·9–119·4°, λ_{max} 2·88 μ (OH), 4·45 (C≡N), 5·85 (C=O).

(Found: C, 63·66; H, 7·28; N, 3·91. $C_{20}H_{27}O_8N$ requires: C, 63·64; H, 7·21).

From later chromatographic fractions, eluted with 25% acetone-petroleum ether, was isolated 0·550 g (2·7%) of the ester-lactone XXI corresponding to hydroxycyanoester XIIIa.

2,3,4-*Trimethoxybenzo-6-carbomethoxymethyl-6-acetoxycycloheptan-5-propionic acid methyl ester*. To 2·5 ml of acetic anhydride, b.p. 136–137°, were added 51·5 mg ($1·25 \times 10^{-4}$ m.) of hydroxydiester from XIVa, m.p. 99–101°, and 2 mg of *p*-toluenesulfonic acid monohydrate. The colorless mixture was heated at 90° for 8 hr.

Thirty millilitres of chloroform was added and this solution was shaken with 10% sodium bicarbonate solution until the acetic anhydride had been decomposed, as evidenced by cessation of carbon dioxide evolution. The chloroform layer was separated and the aqueous solution extracted again. The combined chloroform layers were dried over magnesium sulfate, filtered, and evaporated to yield an oily product which showed no hydroxyl band in the infrared. Chromatography on Alumina using acetone–petroleum ether afforded about 20 mg which crystallized on long standing in the freezer, m.p. 90–100° Recrystallization from petroleum ether afforded colorless prisms, m.p. 100·3–101·1°, λ_{max} 5·8 μ (broad) (C=O), no hydroxyl band. Upon admixture with a sample of hydroxydiester, m.p. 100–101°, the melting point was 80–96°.

(Found: C, 61·13; H, 7·12. $C_{23}H_{32}O_9$ requires: C, 61·04; H, 7·13).

This tertiary acetate could also be prepared by treatment of hydroxydiester with isopropenyl acetate and acid catalyst.

2,3,4-*Trimethoxybenzo-6-carbomethoxymethyl-6-hydroxycycloheptan-5-propionic acid δ-lactone* XVIIIa. The desired lactonization was effected by the use of N,N′-dicyclohexylcarbodiimide. The crude hydroxydiacid from basic hydrolysis of 2·216 g (0·00586 mole) of cyanohydroxy ester XIIIa was used in this experiment. This entire product was dissolved in 15 ml of pyridine, distilled from barium oxide, b.p. 114°, and 1·262 g (0·00614 mole) of N,N′-dicyclohexylcarbodiimide, b.p. 114–115° at 0·3 mm, was added to the solution. Within an hour, N,N′-dicyclohexylurea began to precipitate from the solution. After two days at room temperature the pyridine solution was removed with a capillary dropper. The residue of white needles was washed with ether, and the ether was added to the pyridine solution. The precipitate of the urea weighed 1·235 g (m.p. 232–235°), amounting to 90·0% of the theoretical yield based on N,N′-dicyclohexylcarbodiimide.

The ether–pyridine solution was blown to dryness under a stream of nitrogen and the residue was dried *in vacuo* for 24 hr. After this period there remained 3·123 g, from which no further pyridine could be removed by vacuum drying. This entire product was dissolved in 100 ml of methanol and treated with an excess of freshly distilled ethereal diazomethane. The solvents were removed by distillation to afford an oily residue (2·45 g) which was chromatographed directly on 100 g of alumina. Using an acetone–petroleum ether eluent pair, the remaining dicyclohexylurea was eluted slightly before the desired product, which came off the column with 10% acetone–petroleum ether. Recrystallization of solid fractions from methanol afforded a total of 0·863 g (39·0% from cyanohydroxyester) of large colorless prisms, m.p. 145–148°. Further recrystallization from methanol afforded an analytical sample, m.p. 148·2–148·7°, λ_{max} 5·80 μ (broad).

(Found: C, 63·65; H, 6·98; —OCH_3, 32·91. $C_{20}H_{26}O_7$ requires: C, 63·48; H, 6·93).

This ester lactone was the same compound that had been previously isolated in small yield from the Reformatsky reaction of cyanoketone IX.

Acyloin condensation of ester-lactone XVIIIa. I. *Sodium dispersion in xylene method.* The classical method of running an acyloin condensation, employing dispersed sodium in an inert solvent at elevated temperature, was tried on ester-lactone XVIIIa. A 548 mg (0·00145 mole) sample of the ester-lactone, m.p. 147–149°, was pulverized and dried at 0·1 mm pressure for 48 hr at room temperature.

The apparatus consisted of a 2 l, three-necked flask equipped with a nitrogen inlet, a Vibro-Mischer vibrating high-speed stirrer, and coil condenser, on top of which was placed a Hershberg dropping funnel and a drying tube filled with Drierite. The shaft of the Vibro-Mischer was inserted into the flask through a rubber gasket in a glass sleeve which in turn was set in an appropriately sized cork in the middle neck of the reaction flask.

With a stream of purified nitrogen flowing through the system, 500 ml of xylene, which had been distilled from sodium, b.p. 138–139°, was added to the flask. The last traces of water were removed by refluxing the xylene and distilling out a small portion. The 548 mg sample of dried ester-lactone was placed in the Hershberg dropping funnel, and to it was added, by means of a dried pipette, 50 ml of the distilled xylene.

Approximately 250 mg (0·011 mole) of freshly cut sodium was then added to the flask. With the xylene at reflux, this sodium was dispersed to a fine sand by means of the Vibro-Mischer operating at maximum speed. The xylene solution of ester-lactone was then added to the sodium dispersion over a 2 hr period, allowing each drop to be diluted by the refluxing xylene in the coil condenser. Heating and vibro-mixing were continued for an additional 2 hr, and then the system was allowed to cool completely. Ten milliliters of glacial acetic acid and then a large volume of water were added to the mixture, with stirring. The water layer was separated and the xylene was dried over magnesium sulfate, and filtered.

Careful distillation of the xylene at reduced pressure under nitrogen over a 4 hr period left a residue of only 330 mg. No further material was obtained on slow redistillation of the distillate, and the 330 mg was all the material accounted for.

Chromatography of this product on 10 g of alumina afforded 74 mg (17%) of an impure crystalline substance, m.p. 100–140°, on elution with 5% acetone–petroleum ether. Recrystallization of this material from diisopropyl ether yielded colorless rods, m.p. 140·1–140·6°, λ_{max} 233 mμ (ε = 21,600), λ_{max} 6·05 μ (strong), 6·18 (weak). These spectral properties permitted structural assignment of this compound as the α,β-unsaturated ketone, 2,3,4-trimethoxy-4b,5,6,7,9,10-hexahydro-7-keto-Δ^8-B-homophenanthrene (XXIV).

(Found: C, 71·52; H, 7·52. $C_{18}H_{22}O_4$ requires: C, 71·50; H, 7·34).

Further elution, with 20% acetone–petroleum ether, gave about 80 mg of an amorphous solid which could not be recrystallized into any apparently pure compounds. Material which had been reprecipitated, softening from 90–117°, had λ_{max} 218 mμ (ε = 37,000, based on mol. wt. of 360) 252 (ε = 15,000), broad hydroxyl absorption from 2·9–4·0 μ, carbonyl absorption at 5·8–5·9 μ. This material was subjected to elemental analysis, but the figures obtained did not correspond to a single empirical formula, such as the Dieckmann product suggested by the spectral data.

2,3,4-Trimethoxybenzo-6-carboxymethyl-6-hydroxycycloheptan-5-propionic acid XIVb. The hydroxydiacid related to cyanohydroxyester XIIIb was prepared by basic hydrolysis of the less plentiful Reformatsky isomer in exactly the same manner used to prepare hydroxydiacid XIVa from cyano hydroxyester XIIIa. A solution of 4·394 g (0·01165 mole) of XIIIb in 60 ml of methanol was

added to a solution of 25 g of potassium hydroxide in 100 ml of water and the mixture was heated at reflux for 21 hr. The workup of the reaction mixture was identical to that described above for the stereoisomeric hydroxydiacid, except that in this case, the solid diacid precipitated from the aqueous solution upon acidification. This precipitate was separated and combined with the residue from chloroform extraction for purification by recrystallization from methanol. The total yield of recrystallized material, m.p. 204–207° (dec.), was 4·087 g (91·8%). Further recrystallization from methanol afforded an analytical sample, m.p. 206·0–208·0° (dec.).

(Found C, 59·58; H, 6·71. $C_{19}H_{26}O_8$ requires: C, 59·67; H, 6·85).

Upon treatment of this hydroxydiacid with an excess of distilled ethereal diazomethane the corresponding hydroxydiester was formed. This compound was purified by recrystallization from petroleum ether to afford white needles, m.p. 84·2–85·4°, λ_{max} 2·96 μ (OH), 5·81 μ (C=O).

(Found: C, 61·52; H, 7·44. $C_{21}H_{30}O_8$ requires: C, 61·45; H, 7·37).

2,3,4-*Trimethoxybenzo-6-carbomethoxymethyl-6-acetoxycycloheptan-5-propionic acid methyl ester*. The tertiary acetate derivative of the above hydroxydiester was prepared by both of the methods which similarly converted the isomeric hydroxydiester to the acetate.

In 5 ml of acetic anhydride were placed 217 mg ($5·28 \times 10^{-4}$ mole) of hydroxydiester and 5 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was heated at 95° for 19 hr. The reaction was worked up as before and the crude product was chromatographed on 10 g of alumina. Elution with 2% acetone–petroleum ether afforded about 100 mg of material which crystallized. Recrystallization from petroleum ether afforded 77·0 mg (32·2%) of large, square, colorless plates, m.p. 97–100°. Further recrystallization afforded an analytical sample, m.p. 99·0–99·8°, λ_{max} 5·8 μ (C=O).

(Found: C, 61·16; H, 6·82; —OCH_3, 34·00. $C_{23}H_{32}O_9$ requires: C, 61·04; H, 7·13).

2,3,4-*Trimethoxybenzo-6-carbomethoxymethyl-6-hydroxycycloheptan-5-propionic acid δ-lactone* (XVIIIb). The ester-lactone in the less plentiful diastereoisomeric series was also prepared by the use of N,N′-dicyclohexylcarbodiimide. To a solution of 3·620 g (0·00947 mole) of hydroxydiacid XIVb, m.p. 204–207° (dec.), in 22 ml of dry pyridine was added 2·025 g (0·00984 mole) of purified N,N′-dicyclohexylcarbodiimide. Dicyclohexylurea precipitated within 5 min. After 20 hr at room temperature the reaction was worked up as described in the preparation of ester-lactone XVIIIa. The precipitated dicyclohexylurea amounted to 1·921 g (87·4%), m.p. 230–235°.

The crude lactone-acid residue (5·1 g) was dissolved in methanol and treated with an excess of freshly distilled ethereal diazomethane. After removal of the solvents, the product was chromatographed on 120 g of alumina. Elution with 10–20% acetone–petroleum ether afforded crude crystalline ester-lactone, containing some residual dicyclohexylurea. Recrystallization from acetone–petroleum ether (or, better, from methanol for removal of the urea) afforded 1·458 g (40·7% from the hydroxydiacid) of colorless rods, m.p. 147·5–150°. Further recrystallization from methanol gave an analytical sample, m.p. 149·8–150·3°, λ_{max} 5·80 μ (C=O).

(Found: C, 63·65; H, 6·86; —OCH_3, 32·7. $C_{20}H_{26}O_7$ requires: C, 63·48; H, 6·93; —OCH_3, 32·81).

Acyloin condensation of ester-lactone XVIIIb. I. *Sodium in liquid ammonia method*. A 733 mg ($1·935 \times 10^{-3}$ mole) sample of ester-lactone XVIIIb, m.p. 148·5–150°, was pulverized and dried at 0·1 mm pressure at room temperature for 24 hr. This material was added quickly to 260 ml of anhydrous ether in a dropping funnel which was sealed and allowed to stand, with occasional shaking, for 6 days, which were required for all the ester-lactone to go into solution.

The apparatus consisted of a 1 l, three-necked flask equipped with a glass-paddle stirrer in the center neck, gas inlet tubes for nitrogen and ammonia in one side neck, and provision for the dropping funnel and a dry ice condenser in the third neck. The top of the condenser was open to the atmosphere through a large drying tube containing potassium hydroxide pellets and Ascarite. All equipment was carefully oven-dried and all joints were sealed with clay after the apparatus was assembled. A vigorous stream of purified, dried, nitrogen was passed through the system during the entire setting-up and running of the reaction.

After the assembled system had been flame-dried, 100 ml of anhydrous ether and approximately 150 ml of anhydrous liquid ammonia were introduced into the flask. While the mixture was vigorously stirred, 180 mg ($7·8 \times 10^{-3}$ mole) of sodium, freshly cut under the surface of anhydrous petroleum ether, was added quickly through the ammonia inlet, which was stoppered after the sodium addition. Then the ethereal solution of ester-lactone was added from the dropping funnel over a period of 20 min, during which time a small amount (ca. 30 mg) of this compound crystallized on the tip of the

dropping funnel. The characteristic blue-black color of sodium in liquid ammonia persisted until shortly after completion of the additon of the ester-lactone. A white suspension, containing a small amount of unidentified brown material, remained after the disappearance of the blue-black color.

The ammonia was allowed to evaporate and, when the exit stream of nitrogen from the drying tube no longer turned red litmus blue, 3 ml of methanol in 50 ml of ether was added. After a few minutes the mixture was acidified with 50 ml of 5% hydrochloric acid. The ether layer was separated and the aqueous layer was thoroughly extracted with chloroform. The combined organic extracts were then washed with 5% sodium bicarbonate solution. By acidification of the bicarbonate extract and extraction with chloroform, 70 mg of an oily acidic product was obtained, which was not investigated further.

The original organic extracts were dried over sodium sulfate, filtered, and evaporated to yield 566 mg of a foamy white residue. This product was chromatographed on 20 g of alumina, using the customary acetone–petroleum ether eluent pair.

The first crystalline material to be eluted from the column was a very small amount (7 mg) of the starting material.

The second crystalline substance, also removed from the column with 20% acetone-petroleum ether, was recrystallized from ether–petroleum ether to give 12·5 mg of material melting 165–176° λ_{max} 2·97 μ, 5·90 μ. This material was found to consume 8% of one equivalent of periodate.

Upon elution with 50% acetone–petroleum ether another crystalline substance was obtained. Recrystallization from acetone–petroleum ether afforded 62·7 mg (9·2%) of white needles, m.p. 149–154°, λ_{max} 282 mμ ($\varepsilon = 1200$), λ_{max} 3·0 μ (OH, strong), 5·82 (C=O, weak). Further recrystallization did not change the melting point. This compound was found to consume 70% of one equivalent of periodate, compared to the 85% of an equivalent consumed by benzoin in the parallel control experiment. The subsequent reactions of this substance identified it definitely as the cyclic hemiketal XXV.

No further material was obtained from the column until 25% methanol in acetone was employed as the eluent. A small amount of crystalline material was then eluted, which was recrystallized from acetone–petroleum ether to give 7 mg, m.p. 207–221°, λ_{max} 3·05 μ (strong), 5·7 (weak), 5·85 (weak). This material was found to consume 100% of 1 mole of periodate, but due to lack of material could not be investigated further.

The cyclic hemiketal of 7a-hydroxy-10-*ketodemethoxydesacetamidohexahydrocolchicine* (XXVII). The cyclic hemiketal, 62·7 mg ($1·79 \times 10^{-4}$ mole), m.p. 149–154°, was dissolved in 15 ml of methanol and refluxed for 3 hr with 750 mg of cupric acetate. Within 15 min of the start of the reaction a definite copper-colored precipitate formed. Such a precipitate was not observed when cupric acetate alone was refluxed in methanol. The mixture was diluted with 90 ml of 1 N hydrochloric acid and extracted three times with 40 ml of chloroform. The organic extracts were washed with 10 ml of 1 N hydrochloric acid, 20 ml of dilute sodium bicarbonate solution, 25 ml of water, dried over sodium sulfate, filtered, and evaporated, to yield 65 mg of residue, which readily crystallized upon trituration with ether, m.p. 192–201°, λ_{max} 5·68 μ (strong). Repeated recrystallization from acetone–petroleum ether afforded colorless rods, m.p. 203·0–204·5° (with previous softening, and decomposition).

(Found: C, 65·35; H, 6·78. $C_{19}H_{24}O_6$ requires: C, 65·50; H, 6·94).

Dehydration of the cyclic hemiketal XXVII *with* p-*toluene-sulfonic acid in benzene*. To a solution of 50·3 mg ($1·44 \times 10^{-4}$ mole) of the crude ketone XXVII, m.p. 192–201°, in 100 ml of distilled benzene was added 50 mg of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed connected to a Dean-Stark water separator, allowing benzene to distil gradually until the volume in the reaction flask had been reduced to 50 ml Aliquots of the reaction mixture, diluted with benzene, were examined spectrally periodically. Over a period of 5 hr, a peak at 371 mμ (in benzene) developed steadily until it reached an intensity of $\varepsilon = 13{,}000$. A further 30 min of reflux produced a very slight diminution of this peak and the reaction was halted.

The benzene solution was washed with dilute sodium bicarbonate solution and with water, and these aqueous washes were extracted with chloroform. The combined organic layers were dried over sodium sulfate, filtered, and evaporated under a stream of purified nitrogen. The ultraviolet spectrum of this 50 mg of residue was taken in 95% ethanol, exhibiting λ_{max} 365 ($\varepsilon = 9000$). That this peak was due to the presence in the reaction product of material of structure XXVIII was confirmed by the subsequent facile conversion to the tropolonoid system. Due to the decrease in the intensity of

absorption during workup of the dehydration reaction, the aromatization was undertaken as quickly as possible.

Desacetamidocolchiceine (V). The entire 50 mg of residue from the above acid-catalyzed dehydration was dissolved in 50 ml of chloroform and 25·0 mg ($1{\cdot}40 \times 10^{-4}$ mole) of N-bromosuccinimide, which had been recrystallized from water and dried *in vacuo* over phosphorus pentoxide, was added. The mixture was refluxed for 15 min and then the ultraviolet spectrum of an aliquot was determined. The peak at 365 mμ had completely been replaced by one at 351 mμ ($\varepsilon = 7500$, chloroform solution). Refluxing for an additional hour did not change this spectrum appreciably.

The chloroform solution was washed with water, dried over sodium sulfate, filtered, and evaporated under a stream of nitrogen to yield 53 mg of semi-crystalline residue, which was chromatographed on 1·0 g of silicic acid. With 50% chloroform in carbon tetrachloride a solid substance, m.p. 150–165°, was eluted. By recrystallization from absolute ethanol 3 mg of material, m.p. 165–170°, was isolated.

This material was then compared with desacetamidocolchiceine prepared from natural colchicine by the route described in the Discussion. The melting point of a mixture of totally synthetic desacetamidocolchiceine, m.p. 165–170°, and naturally-derived V, m.p. 168–170°, was 165–170°. The ultraviolet spectra, λ_{max} 244 mμ ($\varepsilon = 35{,}600$), 351 ($\varepsilon = 18{,}400$), and infrared spectra (typical colchicine derivative pattern, doublet at 6·19–6·25 μ, λ_{max} 6·46 μ, etc.) were identical. The intensity of absorption at 351 mμ in the reaction mixture, $\varepsilon = 7500$, indicated approximately a 40% conversion of ketone XXVII to desacetamidocolchiceine.

The methyl ethers of desacetamidocolchiceine. A solution of 5·00 g (0·0152 mole) of purified desacetamidocolchiceine, m.p. 167–170°, in 200 ml of methanol was treated with an excess of freshly distilled ethereal diazomethane. Completion of the reaction was indicated when the solution no longer gave a dark green ferric chloride test in ethanol. The solvents were removed by distillation, and 350 ml of ether was added to the oily residue. After standing overnight 2·10 g (40·3%) of tan clusters, m.p. 179–184°, had separated from solution. Recrystallization of this methyl ether, desacetamidocolchicine, from acetone–petroleum ether afforded greenish-yellow plates, m.p. 183·6–184·1°.

(Found: C, 70·20; H, 6·56. $C_{20}H_{23}O_5$ requires: C, 70·16; H, 6·48).

Upon allowing the ethereal mother liquors to evaporate, 2·02 g of a crystalline mixture was obtained. Recrystallization of this material from an ether-diisopropyl ether solvent pair containing a little acetone yielded 0·801 g of light tan flakes, m.p. 147–149°. From the mother liquors an additional 0·465 g, m.p. 146·5–149°, was obtained by fractional crystallization, aided by manual separation of the fine flakes of lower-melting ether from the darker, thicker crystals of higher-melting ether. The total yield was 1266 mg (24·3%) of purified desacetamidoisocolchicine. An analytical sample, m.p. 148·0–148·7°, was prepared by recrystallization from ether containing a little acetone.

(Found: C, 69·81; H, 6·77. $C_{20}H_{23}O_5$ requires: C, 70·16; H, 6·48).

The entire mother liquors from both isomers, as well as most of the higher-melting ether, were reconverted to desacetamidocolchiceine by aqueous acid hydrolysis in order to furnish material for remethylation to obtain more of the desired lower-melting ether.

Reaction of desacetamidoisocolchicine with N-bromosuccinimide. The bromination of the lower-melting methyl ether was first performed successfully by Eschenmoser[10], and a description of the reaction is included here which differs only slightly from that reported by him and his coworkers.

To a solution of 592 mg (0·00173 mole) of the lower-melting ether, m.p. 147–148°, in 35 ml of hot carbon tetrachloride was added 308 mg (0·00173 mole) of N-bromosuccinimide which had been recrystallized twice from water and dried *in vacuo* over phosphorus pentoxide. While the reaction flask was irradiated with ultraviolet light, the mixture was heated at reflux and stirred magnetically for 23 min, which was the time required for all the solid N-bromosuccinimide to go into solution.

The mixture was allowed to stand at room temperature for 1 hr and then the precipitate of succinimide was separated by filtration. After being washed with carbon tetrachloride and dried, the precipitate weighed 126 mg, or 73·7% of the theoretical amount. The filtrate was partitioned between chloroform and water, and the water layer was extracted further with chloroform. The organic layers were dried over sodium sulfate, filtered, and evaporated to yield a light yellow oil, which crystallized upon trituration with acetone. By rapid washing of these crystals with acetone there was obtained 125 mg of solid residue, m.p. 110–160°. This material was purified by recrystallization from acetone–petroleum ether to give 89 mg (12·2%), m.p. 158–164°. That this compound was the desired bromination product was indicated by the fact that it gave a strong positive test for active bromine within a few seconds of the addition of alcoholic silver nitrate solution.

Six further recrystallizations from acetone–petroleum ether afforded yellow rods, m.p. 161·0–163·5° (with decomposition). Eschenmoser[10] reported m.p. 165°. From one preparation material giving a positive silver nitrate test was isolated which had m.p. 164–170°.

(Found: C, 56·54; H, 4·91; Br, 18·86. $C_{20}H_{21}O_5Br$ requires: C, 57·02; H, 5·03; Br, 18·97).

The mother liquors from the acetone wash crystallized on standing and yielded another reaction product, m.p. 190–207°. Recrystallization from acetone–petroleum ether afforded bright yellow needles, m.p. 218–222° (dec.), which gave a negative silver nitrate test, and was undoubtedly the same nuclear bromination product obtained by Eschenmoser[10], reported m.p. 212°.

7-*Azidodesacetamidoisocolchicine* (XXXV). A solution of 56 mg ($1·33 \times 10^{-5}$ mole) of the bromo compound XXXV, m.p. 163–168°, in 10 ml of methanol and 34 mg ($5·2 \times 10^{-4}$ mole) of activated sodium azide were heated in a sealed tube at 90–95° in a water bath for 27 hr. After this time the tube was opened and the contents, which had not changed in appearance from their original light yellow color, were partitioned between water and chloroform. The organic layer was dried over sodium sulfate, filtered, and evaporated, leaving a crystalline residue, m.p. 155–168°, weighing 53 mg (theoretical 51 mg). This product gave a negative test for active bromine with alcoholic silver nitrate, indicating complete reaction of the benzylic bromine. Recrystallization from acetone–petroleum ether gave material melting at 166–169°, λ_{max} 4·72 μ (65%). An analytical sample, m.p. 167–169·5° (dec.) was obtained by four further recrystallizations from acetone–petroleum ether.

(Found: C, 62·80; H, 5·88; N, 10·56. $C_{20}H_{21}O_5O_3$ requires: C, 62·65; H, 5·52; N, 10·96).

Racemic trimethylcolchicinic acid (XXIX). The azide XXXVI was converted to (±) trimethylcolchicinic acid in two steps without purification of the intermediate desacetylisocolchicine.

The azide, 21 mg ($5·5 \times 10^{-5}$ mole), m.p. 166–169°, was mixed with an equal weight of 10% palladium-on-carbon in 10 ml of methanol and hydrogenated for 10 min at atmospheric pressure and room temperature. The mixture was filtered through Filtercel and the filtrate was evaporated under a stream of nitrogen to a yield 20 mg of semi-crystalline residue. The infrared spectrum of this product showed no band at 4·72 μ, indicating complete hydrogenolysis of the azide group, and it was assumed that the product consisted primarily of desacetylisocolchicine.

This material was hydrolyzed to the free tropolone under conditions similar to those used for the conversion of colchicine to colchiceine. The combined crude reduced products, 44 mg, were heated at reflux in 10 ml of 1·0 N hydrochloric acid for 2 hr. A positive dark green ferric chloride test, indicating the presence of free tropolone, developed within a few minutes of starting the acid treatment.

The aqueous mixture was brought to a pH of 7·5 (pH paper was used as indicator) with dilute sodium bicarbonate solution and extracted with chloroform. The organic layer was dried over sodium sulfate, filtered, and evaporated to yield 40 mg of partially crystalline material, m.p. 210–240° (dec.). The entire product was purified by chromatography on 2·0 g of silicic acid, using chloroform and 2% methanol in chloroform as eluents, to yield crystalline fraction weighing 16 mg. Recrystallization of these fractions from absolute ethanol afforded bright yellow powdery crystals, m.p. 240–244° (dec.).

This synthetic racemic trimethylcolchicinic acid was compared with an authentic sample prepared by the method of Corrodi and Hardegger[49]. A mixture of synthetic XI, m.p. 240–244° (dec.), and naturally-derived acid, m.p. 242–246° (dec.), had a melting point of 240–246° (dec.). The ultraviolet spectra, λ_{max} 242 mμ (ε = 31,000), 353 (ε = 19,000), shoulder at 230 (ε = 27,000), and infrared spectra (potassium bromide pellets) of the two samples were identical.

2,3,4-*Trimethoxybenzo*-6-*carboxymethyl*-6-*hydroxycycloheptan*-5-*propionic acid* (XIVa). Hydroxycyanoester XIIIa was converted to the hydroxydiacid by strong basic hydrolysis. A solution of 11·255 g (0·0298 mole) of the more plentiful hydroxycyanoester in 100 ml. of methanol was added to a solution of 50 g of potassium hydroxide in 200 ml of water and the mixture was heated at reflux for 24 hr. Most of the methanol was then distilled from the reaction mixture. The basic solution was made acid to Congo red indicator by the addition of dilute hydrochloric acid, causing separation of an oil. This oil was taken up in chloroform and the aqueous solution was extracted thoroughly with chloroform. The organic layers were dried over sodium sulfate, filtered, and evaporated to give a colorless oil which readily crystallized in fine white needles from acetone–petroleum ether. After one recrystallization there was obtained 10·790 g (94·7%) of material which softened to a colorless oil with apparent decomposition from 80–90°. Further recrystallization did not change this melting point behavior.

(Found: C, 59·65; H, 6·90. $C_{19}H_{26}O_8$ requires: C, 59·67; H, 6·85).

Upon treatment of this hydroxydiacid with an excess of distilled ethereal diazomethane the

corresponding hydroxydiester was formed. This compound was readily purified by recrystallization from petroleum ether to afford white needles, m.p. 100·6–101·4°. λ_{max} 2·90 μ (OH), 5·85 μ (C=O).

(Found: C, 61·37; H, 7·36. $C_{21}H_{30}O_8$ requires: C, 61·45; H, 7·37).

N,N-*Dimethyldeacetylcolchiceine hydroiodide*. A modification of a method described by Kiselev and Men'shikov[29] was employed in the preparation of the N,N-dimethyl hydroiodide of trimethylcolchicinic acid. To a 100 ml round-bottom flask, equipped with a thermometer and a condenser attached to a mercury trap, was added 2·096 g (0·0061 mole) of trimethylcolchicinic acid, m.p. 159–161·5°, 40 ml. of purified dioxane, and 10 ml (0·161 mole) of methyl iodide. The flask containing the homogeneous mixture was placed in a previously heated oil bath, seeded and heated at just below reflux temperature (74°). Within 30 min product began to separate from the solution. After an additional 23·5 hr the mixture was allowed to cool to room temperature and allowed to stand overnight. The precipitate was separated by filtration, washed with purified dioxane and dried to constant weight in air to give 1·551 g of poorly formed yellow plates, m.p. 200–220°. Crystallization from 40 ml of absolute ethanol afforded 0·964 g (31·6% of theory) of golden yellow plates, m.p. 250–252° dec.

Two recrystallizations of a specimen from a similar experiment gave yellow plates, m.p. 254–256° dec.

(Found: C, 50·61; H, 5·23. $C_{21}H_{26}NO_5I$ requires C, 50·53; H, 5·25).

N,N,N-*Trimethylcolchicinic acid iodide* (XXXI). To a solution of 0·964 g (0·00193 mole) of the tertiary amine hydroiodide, m.p. 250–252° dec., in 50 ml of water and 50 ml of chloroform was added 13·18 ml of 0·147 N aqueous sodium hydroxide (0·00193 equiv.). The mixture was shaken thoroughly and the chloroform layer separated. The aqueous layer was extracted two additional times with 50 ml portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue, a brown glass, was dissolved in 40 ml of purified dioxane and after the addition of 10 ml (0·16 mole) of purified dioxane was heated, as in the preceding experiment, at 74°. After 2 hr product began to separate. The reaction mixture was heated at 74° for an additional 40 hr after which time it was cooled to room temperature and allowed to stand overnight. The product was separated by filtration, washed with purified dioxane and dried in air to give 0·865 g (87·4% of theory) of well formed light olive colored prisms, m.p. 231·5–235·5° dec. A sample twice recrystallized from absolute ethanol and dried for 18 hr at 25° (0·1 mm) was obtained as light olive colored prisms, m.p. 231·8–235·4° dec., λ_{max}^{EtOH} 219, 244 and 358 mμ.

(Found: C, 51·30; H, 5·68. $C_{22}H_{28}NO_5I$ requires: C, 51·47; H, 5·50).

Desacetamidocolchiceine. Hydrogenolysis of the quaternary ammonium iodide was effected by a procedure suggested by the work of Bernauer, Schmid and Karrer[40]. A solution of 4·758 g (0·00928 mole) of the quaternary ammonium iodide, m.p. 231–236° in 130 ml of 0·385 N aqueous sodium hydroxide (0·05 mole) was hydrogenated at atmospheric pressure and room temperature over 1·0 g of pre-equilibrated 10% palladium on-carbon catalyst. After 1 hr 1·0 mole-equiv of hydrogen (0·0093 mole) had been absorbed and hydrogen uptake had ceased. The mixture was filtered, the filtrate acidified with glacial acetic acid and thoroughly extracted with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to yield a light brown oil which spontaneously crystallized to a slightly oily solid. Crystallization of the crude product from absolute ethanol afforded 2·095 g of olive colored prisms, m.p. 168–170·5°. Concentration of the filtrate gave a second crop of 0·168 g, m.p. 167·5–168·5°. A third crop amounting to 0·065 g, m.p. 167·8–169°, was obtained thus affording a total of 2·329 g (76·7% of theory) of product.

Three recrystallizations from absolute ethanol of a specimen obtained from a similar experiment gave golden prisms, m.p. 169·3–170·5°, λ_{max}^{EtOH} 245 mμ (log ε 4·55) and 351 mμ (log ε 4·26).

(Found: C, 69·38; H, 6·09. $C_{19}H_{20}O_5$ requires: C, 69·50; H, 6·14).

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BIOGENESIS OF THE RAUWOLFIA ALKALOIDS—II

THE INCORPORATION OF TRYPTOPHAN INTO SERPENTINE AND RESERPINE

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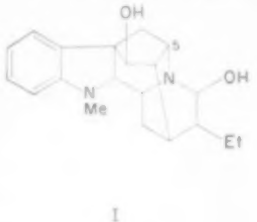
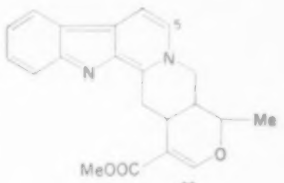
Abstract—Radioactive serpentine which was obtained from *Rauwolfia serpentina* plants which had been fed tryptophan-2-C^{14} was degraded systematically and was found to be labeled solely at C-5. This result indicates that tryptophan is a direct precursor of the β-carboline moiety of this alkaloid. Radioactive reserpine which was obtained from the same feeding experiment was labeled only on the reserpic acid part of the alkaloid.

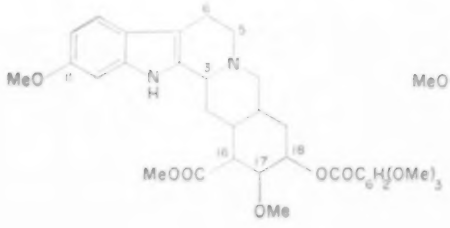
WE have previously reported[1] that the administration of DL-tryptophan-2-C^{14} to *R. serpentina* plants (3 years old) led to the formation of radioactive ajmaline (I), serpentine (II) and reserpine (III). We chose to degrade the ajmaline first since it is the most abundant alkaloid in *R. serpentina* and had the highest specific activity.



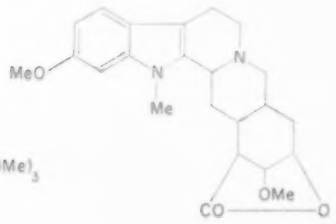
I



II



III



IV

Our results[1] indicated conclusively that the ajmaline was labeled solely at C-5. This result was in agreement with previously conceived hypotheses on the biogenesis of ajmaline.[2,3] It was a reasonable assumption that serpentine and reserpine would also be specifically labeled at C-5 of their β-carboline moieties. Therefore our initial experiments were directed towards the conversion of these alkaloids to simple derivatives of harman which could be degraded by the procedure previously worked out for the

[1] E. Leete, *J. Amer. Chem. Soc.* **82**, 6338 (1960).
[2] R. B. Woodward, *Angew. Chem.* **68**, 13 (1956).
[3] R. Robinson, *Festschrift Arthur Stoll* p. 457. Birkhäuser, Basel (1957).

degradation of the radioactive ajmaline. Ajmaline yielded N-(ind)-methylharman (VI) on heating with sodalime at 360°,[4] but serpentine failed to yield any harman under similar conditions. However since Leonard and Elderfield[5] obtained harman by the fusion of alstonine with potassium hydroxide, it seemed reasonable to expect that the same compound would be obtained from serpentine since the two alkaloids are stereoisomers. This proved to be the case, a 20 per cent yield of harman being obtained. The harman which had the same specific activity as the serpentine was methylated according to the procedure of Potts and Saxton[6] to yield N-(ind)-methylharman. Subsequent degradation proceeded as illustrated in Fig. 1 and is identical with that used for the N-(ind)-methylharman derived from the radioactive ajmaline. In our earlier

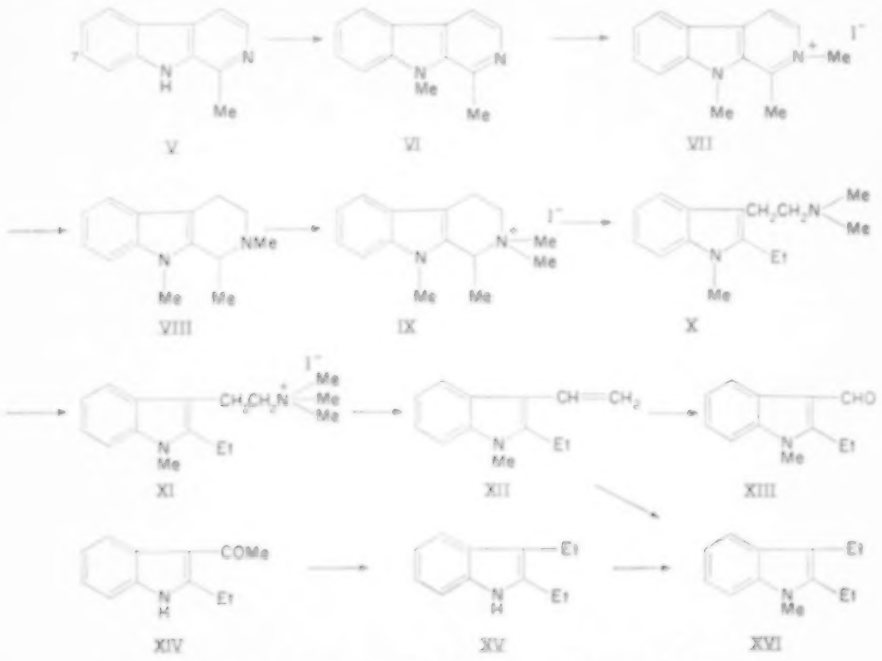


FIG. 1. Degradation of the harman derived from serpentine and related reactions.

paper[1] we made no attempt to characterize the 2-ethyl-1-methyl-3-vinyl-indole (XII) obtained by the Hofmann degradation of 2-ethyl-1-methyl-N, N-dimethyltryptamine methiodide (XI). Its structure was assigned on the basis of its mode of formation and its subsequent oxidation with osmium tetroxide and periodate to 2-ethyl-1-methyl-3-indole aldehyde and formaldehyde. We have now found that a freshly prepared sample analyzed correctly and yielded a stable 1,3,5-trinitrobenzene derivative. The ultraviolet spectrum of theis 3-vinyl indole is illustrated in Fig. 2, together with its hydrogenation product, 2,3-diethyl-1-methyl-indole. The pronounced absorption at 265 mμ is thus assignable to the 3-vinyl indole chromophor. It is of interest to note that this absorption had decreased 50 per cent in a sample of the vinylindole

[4] F. A. L. Anet, D. Chakravarti, R. Robinson and E. Schlittler, *J. Chem. Soc.* 1242 (1954).
[5] N. J. Leonard and R. C. Elderfield, *J. Org. Chem.* 7, 556 (1942).
[6] K. T. Potts and J. E. Saxton, *J. Chem. Soc.* 2641 (1954).

which was 12 hours old, presumably indicating extensive polymerization. 2,3-Diethyl-1-methylindole (XVI) was prepared for comparison with the hydrogenation product of the vinylindole as follows. 2-Ethylindole was refluxed with a mixture of acetic acid and acetic anhydride to yield 3-acetyl-2-ethylindole (XIV). This ketone was reduced[7] with

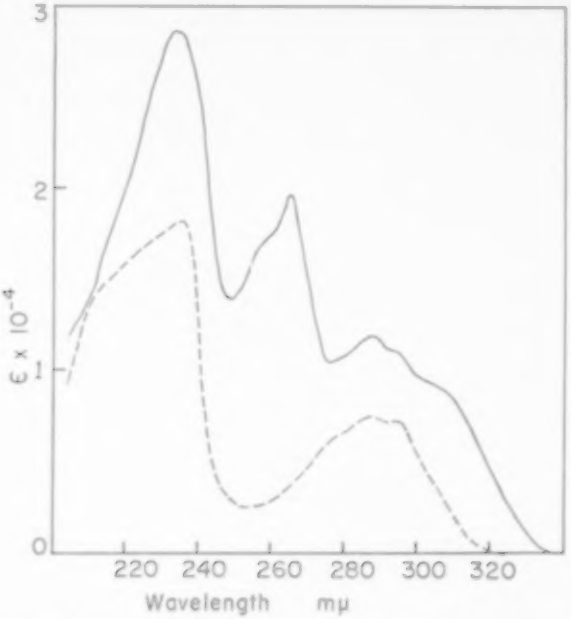


FIG. 2. Ultraviolet spectra in 95% ethanol of 2-ethyl-1-methyl-3-vinylindole (XII) [full line] and 2,3-diethyl-1-methyl indole (XVI) [broken line].

lithium aluminum hydride to 2,3-diethylindole which was methylated[6] to yield XVI. The activities of serpentine and its degradation products are recorded in Table 1. It is seen that the 2-ethyl-1-methyl-3-indole aldehyde was inactive whereas all the other degradation products had essentially the same specific activity as the serpentine indicating that all the activity was located at C-5 of the serpentine molecule. This result strongly suggests that tryptophan is a direct precursor of the β-carboline moiety of this alkaloid, in agreement with previous hypotheses.[8]

Our attempts to convert reserpine to simple derivatives of harman or harmine (7-methoxyharman) have not so far been successful. Basic hydrolysis of the radioactive reserpine yielded 3,4,5-trimethoxybenzoic acid which was completely inactive and reserpic acid which had the same specific activity as the reserpine. Fusion of reserpic acid with potassium hydroxide or heating with sodalime failed to yield any harmine. When reserpine was dissolved in liquid ammonia containing sodamide and treated with methyl iodide two compounds were isolated from the reaction mixture, 3,4,5-trimethoxybenzamide and a compound melting at 219–220°. This compound had no absorption in the NH region of the infrared spectrum but had a strong absorption at 1775 cm^{-1} assignable to a carbonyl group in a γ-lactone. The properties of

[7] *cf.* E. Leete and L. Marion, *Canad. J. Chem.* **31**, 775 (1953).
[8] *cf.* R. Robinson, *The Structural Relations of Natural Products* p. 100. Clarendon Press, Oxford (1955).

this compound are consistent with formula IV, i.e. N-(ind)-methylreserpic acid lactone. The formation of these two compounds is readily rationalized. Attack by amide ions on the ester carbonyl at C-18 yields 3,4,5-trimethoxybenzamide and generates an alkoxide ion which attacks the ester carbonyl at C-16 eliminating an ethoxide ion and

TABLE 1. ACTIVITIES OF SERPENTINE, RESERPINE AND THEIR DEGRADATION PRODUCTS

	Activity* (counts/min per mmole)
Serpentine (II)	$1{\cdot}2 \times 10^6$
Serpentine nitrate	$1{\cdot}1 \times 10^6$
Harman (V)	$1{\cdot}1 \times 10^6$
N-(ind)-Methyl-1,2-dimethyl-1,2,3,4-tetrahydro-β-carboline-N_β-methiodide (IX)	$0{\cdot}9 \times 10^6$
2-Ethyl-1-methyl-N, N-dimethyltryptamine methiodide (XI)	$1{\cdot}2 \times 10^6$
2-Ethyl-1-methyl-3-indole aldehyde (XIII)	0
Formaldehyde dimedone derivative	$1{\cdot}1 \times 10^6$
Reserpine (III)	$5{\cdot}4 \times 10^5$
Reserpine perchlorate	$5{\cdot}5 \times 10^5$
Reserpic acid hydrochloride	$5{\cdot}3 \times 10^5$
3,4,5-Trimethoxybenzoic acid	0

* Radioactivity determinations were carried out in a Nuclear-Chicago Model D-47 Q-gas flow counter using a micromil window. Determinations were carried out on samples of finite thickness, making corrections for efficiency and self absorption.

producing the γ-lactone. Methylation of the indolic nitrogen then yields IV. Fusion of the lactone IV with potassium hydroxide failed to yield any N-(ind)-methylharmine.

Reserpine was dehydrogenated to 3,4,5,6-tetradehydroreserpine with maleic acid in the presence of palladium.[9] However, potassium hydroxide fusion of the tetradehydroreserpic acid obtained by hydrolysis of this compound failed to yield any harmine.

It is of interest to compare the incorporation of radioactivity into the alkaloids of *R. serpentina*. One common method of making such a comparison is by means of the "Percentage Incorporation". This is the total activity found in the alkaloid divided by the total activity fed to the plant. This value is not useful as a basis for comparison in this case since the alkaloids were not recovered quantitatively from the plant and they occur in unequal amounts. It is more meaningful to compare the "Dilution", which is the specific activity of the adminstered tryptophan-2-C^{14} divided by the specific activity of the isolated alkaloid. These results are recorded in Table 2. It is seen that the greatest dilution has occurred with the reserpine. There are many possible explanations for this result and a great deal more work will have to be done before we can account for this. Thus one would have to carry out feeding experiments with plants of different ages in order to determine whether the alkaloids are being produced at different rates at different stages in the development of the plant. The lower incorporation into reserpine could also be related to the presence of the methoxyl group at C-11,

[9] E. Wenkert, E. W. Robb and N. V. Bringi, *J. Amer. Chem. Soc.* **79**, 6570 (1957); *cf.* also *Ibid.* **81**, 2494 (1959).

which is absent in ajmaline and serpentine. At this time we have no information on the mechanism of hydroxylation at this position, and we do not know at which stage in the biogenesis of reserpine this occurs. It would be of interest to isolate deserpidine (reserpine lacking the 11-methoxyl group) and compare its activity with that of

TABLE 2. COMPARISON OF THE INCORPORATION OF TRACER INTO THE ALKALOIDS OF *R. serpentina*

	Weight (mg)	Activity (counts/min per mmole)	Percentage incorporation	Dilution
Ajmaline	80	$2{\cdot}5 \times 10^6$	0·25	710
Reserpine	44	$5{\cdot}4 \times 10^5$	0·018	3300
Serpentine	5·7*	$1{\cdot}2 \times 10^6$	0·007	1500

* Isolated as the nitrate.

reserpine. Questions such as these will occupy the attention of those studying the biogenesis of alkaloids and other natural products for many years to come.

EXPERIMENTAL

Melting points are corrected. The petroleum ether had b.p. 60–80°.

Degradation of the radioactive serpentine

The radioactive serpentine nitrate (5·7 mg) which had been isolated from the *R. serpentina* plants, which had been fed DL-tryptophan-2-C^{14} (37·5 mg, total activity $2{\cdot}2 \times 10^8$ counts/min), was mixed with inactive serpentine hydrochloride (472 mg), dissolved in hot water and neutralized with sodium carbonate. The yellow precipitate of serpentine was crystallized from ethanol until it had a constant specific activity. A small sample was converted to the nitrate as a check on its radiochemical purity.

The diluted serpentine (333 mg) was powdered in a mortar with potassium hydroxide (8·0 g). The intimate mixture was fused in a nickel crucible and heated with stirring in an atmosphere of nitrogen in a metal bath maintained at 360° for 40 min. The contents of the crucible were allowed to cool and ice added. The dark brown solution was extracted several times with ether. The dried ether extract was evaporated to small bulk and ethanolic hydrochloric acid added when a pale brown precipitate of crude harman hydrochloride (100 mg) separated. This hydrochloride was dissolved in water, made basic with sodium hydroxide and extracted with benzene. The dried benzene solution was chromatographed on alumina (activity III) eluting first with benzene and then with 10% ethanol in benzene when the harman was obtained. The harman was further purified by sublimation (200°, 0·001 mm) and the pale yellow sublimate crystallized from a mixture of benzene and petroleum ether to yield harman (34 mg, 20% yield), m.p. 237–238° identical (I.R. spectrum and mixed m.p.) with authentic material. The harman was converted to N-(ind)methylharman by dissolving in liquid ammonia containing sodamide and then adding methyl iodide.[6] The degradation then proceeded through to 2-ethyl-1-methyl-3-indolealdehyde (XIII) and the dimedone derivative of formaldehyde as described in Part I of this series.[1] The specific activity of serpentine and its degradation products are recorded in Table 1 and are calculated for carrier-free material.

2-Ethyl-1-methyl-3-vinylindole (XII)

This vinylindole was obtained as previously described[1] from 2-ethyl-1-methyl-N, N-dimethyltryptamine methiodide. The freshly prepared and redistilled vinylindole was obtained as a colorless liquid (Found: C, 84·20; H, 8·15; N, 7·84. $C_{13}H_{15}N$ requires: C, 84·28; H, 8·16; N, 7·56%). The ultraviolet spectrum in 95% ethanol is recorded in Fig. 2. Its infrared spectrum as a liquid film had a strong absorption at 1625 cm^{-1} which may be assigned to the stretching vibration of the vinyl group since this absorption is absent in its hydrogenation product, 2,3-diethyl-1-methylindole. The

1,3,5-trinitrobenzene complex of 2-ethyl-1-methyl-3-vinylindole was obtained from methanol as violet-brown prismatic needles, m.p. 135–136° (Found: C, 57·33; H, 4·64. $C_{19}H_{18}O_6N_4$ requires: C, 57·28; H, 4·55%).

2,3-*Diethyl-1-methylindole* (XVI)

(a) *From 2-ethyl-1-methyl-3-vinylindole.* The vinylindole (80 mg) was dissolved in absolute ethanol (50 ml) and hydrogenated at 2 atm press in the presence of platinum oxide (40 mg) for 2 hr. The filtered solution was evaporated and the residue distilled *in vacuo* (160°, 0·01 mm) to yield *2,3-diethyl-1-methyl-indole* as a colorless oil, n_D^{27} 1·5724 (Found: C, 83·12; H, 9·15; N, 7·30. $C_{13}H_{17}N$ requires: C, 83·37; H, 9·15; N, 7·48%). Its ultraviolet spectrum in 95% ethanol is recorded in Fig. 2. The *1,3,5-trinitrobenzene complex of 2,3-diethyl-1-methylindole* was obtained as bright red prismatic needles from methanol, m.p. 84–85° (Found: C, 56·89; H, 5·15; N, 13·86. $C_{19}H_{20}O_6N_4$ requires: C, 56·99; H, 5·04; N, 13·99%).

(b) *From 2-Ethylindole: 3-Acetyl-2-ethylindole.* 2-Ethylindole[10] (30 g) was refluxed in a nitrogen atmosphere with a mixture of acetic acid (20 ml) and acetic anhydride (150 ml) for 20 hr. The bulk of the solvent was removed under reduced pressure and the dark brown residue diluted with ethanol when the crude product separated out (15 g). Several crystallizations from ethanol (charcoal) yielded 3-acetyl-2-ethylindole as small colorless prisms, m.p. 159–160° (Found: C, 77·17; H, 7·17; N, 7·62. $C_{12}H_{13}ON$ requires: C, 76·97; H, 7·01; N, 7·48%). Its infrared spectrum (KBr pellet) had a carbonyl absorption at 1627 cm^{-1}.

2,3-Diethylindole. 3-Acetyl-2-ethylindole (1·87 g) was suspended in ether (250 ml) and a solution of 4% lithium aluminum hydride in ether (30 ml) added and the mixture refluxed for 20 hr. Water was then added to the cooled mixture which was filtered, dried and evaporated. The residue was distilled (160° 0·01 mm) to yield *2,3-diethylindole* (1·56 g) as a colorless oil having a strong violet fluorescence, n_D^{27} 1·5829.[11] On prolonged cooling the liquid solidified to a colorless crystalline solid, m.p. 29–30° (Found: C, 82·96; H, 8·62; N, 8·25. $C_{12}H_{15}N$ requires: C, 83·19; H, 8·73; N, 8·09%). The *1,3,5-trinitrobenzene complex of 2,3-diethylindole* was obtained as brownish red prismatic needles from methanol, m.p. 135–136° (Found: C, 55·78; H, 4·65; N, 14·70. $C_{18}H_{18}O_6N_4$ requires: C, 55·95; H, 4·70; N, 14·50%). The *picrate of 2,3-diethylindole* was obtained as dark brown prisms from ethanol, m.p. 135–136° (Found: C, 53·87; H, 4·57; N, 13·83 $C_{18}H_{19}O_7N_4$ requires: C, 53·73; H, 4·51; N, 13·93%).

2,3-Diethyl-1-methylindole. Sodium (150 mg) was dissolved in liquid ammonia (200 ml) containing a small crystal of ferric nitrate. When the blue color had disappeared 2,3-diethylindole (665 mg) dissolved in liquid ammonia was added and an orange solution was obtained. Methyl iodide (0·5 ml) was added and the ammonia allowed to evaporate. Water was added to the residue and the mixture extracted with ether. The dried ether extract was evaporated and distilled (160°, 0·01 mm) to yield 2,3-diethyl-1-methylindole, having an infrared spectrum identical with the material obtained from the vinylindole XII.

Degradation of the radioactive reserpine

(a) *Hydrolysis.* The active reserpine (44 mg) was diluted with inactive material (300 mg) and crystallized from a mixture of methanol and acetone until it had a constant specific activity. A further check on its radiochemical purity was obtained by the preparation of reserpine perchlorate. The diluted reserpine was hydrolysed with sodium hydroxide in aqueous methanol according to established methods,[12] yielding 3,4,5-trimethoxybenzoic acid and reserpic acid which was isolated as its hydrochloride. The activity of reserpine and its degradation products are recorded in Table 1.

(b) *Attempted N-methylation of reserpine.* Reserpine (300 mg) was added to a solution of sodium (40 mg) in liquid ammonia (200 ml). When all the reserpine had dissolved methyl iodide (0·1 ml) was added and the ammonia then allowed to evaporate. Water was added to the residue and the mixture

[10] A. Verley and J. Beduwé, *Bull. Soc. Chim. Fr.* [4] **37,** 190 (1925).

[11] V. F. Martynov and V. F. Martynova [*Zh. Obshchei Khim.* **24,** 2146 (1954); *Chem. Abstr.* **50,** 287 (1956)] describe 2,3-diethylindole as a liquid having n_D^{29} 1·5806 and affording a picrate, m.p. 121–122°. The product obtained by A. E. Arbuzov and I. A. Zaitzev [*Trans. Butlerov Inst. Chem. Tech. Kazan* No. 1, 33 (1934); *Chem. Abstr.* **29,** 4006 (1935)] by the cyclization of the phenylhydrazone of ethylpropylketone was either 2,3-diethylindole or 3-methyl-2-propylindole. Since their compound yielded a picrate, m.p. 144°, it seems likely that the latter indole was obtained.

[12] N. Neuss, H. E. Boaz and J. W. Forbes, *J. Amer. Chem. Soc.* **76,** 2463 (1954).

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extracted with chloroform. The dried chloroform extract was evaporated and the residue dissolved in ethanol (2 ml), diluted with benzene (20 ml) and chromatographed on alumina (activity III). Elution with benzene containing 10% ethanol yielded a pale yellow solid which on crystallization from benzene-petroleum ether gave small colorless prisms (70 mg) of N-(*ind*)-*methylreserpic acid lactone* (IV), m.p. 219–220° (Found: C, 69·28; H, 7·18; N, 7·09. $C_{23}H_{28}O_4N_2$ requires: C, 69·67; H, 7·12; N, 7·07%). Its infrared spectrum had no absorption in the NH region, but had a strong absorption at 1775 cm^{-1} assignable to the carbonyl in a γ-lactone. Further elution of the alumina column with absolute ethanol yielded 3,4,5-trimethoxybenzamide (25 mg), m.p. 182–183°, identical (I.R. spectrum and mixed m.p.) with an authentic specimen. (Found: C, 56·54; H, 6·31; N, 6·67. Calc. for $C_{10}H_{13}O_4N_2$: C, 56·86; H, 6·20; N, 6·63%).

Acknowledgements—This investigation was supported by a research grant MY-2662, from the National Institute of Mental Health, Public Health Service. The author thanks Dr. J. E. Campion of the Riker Laboratories, California and Dr. W. I. Taylor of Ciba Inc., New Jersey, for generous samples of serpentine and reserpine. Analyses were carried out by Mrs. Olga Hamerston and her assistants at the University of Minnesota.

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THE STRUCTURE AND SYNTHESIS OF LIRIODENINE, A NEW TYPE OF ISOQUINOLINE ALKALOID

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(*Received* 27 *December* 1960)

Abstract—Liriodenine (III) is recognised to be a representative of a new class of isoquinoline alkaloid belonging to the aporphine subgroup. A synthetic procedure for this type of alkaloid is developed and applied to the specific case of liriodenine, the key step being the Pschorr cyclization of 1-2′-aminobenzoyl-6,7-methylenedioxyisoquinoline.

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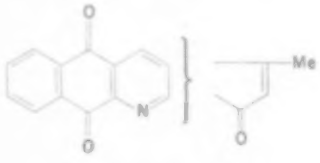
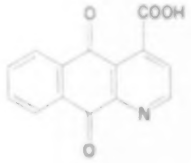
THE tulip tree (*Liriodendron tulipifera* L.) is widely distributed throughout the eastern part of the United States. It finds use as an ornamental tree, and also because of the yellow color of the heartwood is useful for lumber. This color is to its disadvantage however for the groundwood pulp prepared from the wood. The source of this yellow color has been traced[1] to at least two alkaloids. One of them, liriodenine, $C_{17}H_9O_3N$, was examined in detail and evidence was presented in support of the structure I. The presence of three of the rings in liriodenine was considered to have been established by its oxidation to a benzo[g]quinoline-5,10-dione carboxylic acid which is, in our opinion, II (see below). Upon heating it decarboxylated to furnish the known aza-anthraquinone (II; COOH═H). The nature of the remaining ring was not determined but was inferred from the formation of an oxime, the suggested presence of a methyl group (I.R.), and the lack of a hydroxyl, methylenedioxy or methoxyl in the alkaloid.

Buchanan and Dickey recognized, in proposing the structure I for liriodenine, that it was a very unusual one for a natural product. In fact only one other case was quoted, *viz.* phomazarine[2] isolated from the mould, *Phoma terrestris*. In this connection a recent attempt[3] to reisolate this pigment led not to phomazarine but to the polyhydroxyanthraquinone, cynodotin.



I



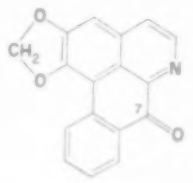
II

We felt that the published evidence for the structure of liriodenine could be interpreted differently. On the basis of formula I for the alkaloid, it seemed strange that oxidation should have produced a monocarboxylic acid rather than a dicarboxylic

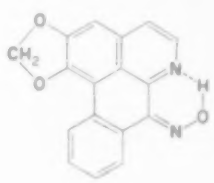
[1] M. A. Buchanan and E. E. Dickey, *J. Org. Chem.* **25**, 1389 (1960).
[2] F. Kögl and J. Sparenburg, *Rec. Trav. Chim.* **59**, 1180 (1940); F. Kögl and F. S. Quackenbush, *Ibid.* **63**, 251 (1944).
[3] D. E. Wright and K. Schofield, *Nature, Lond.* **188**, 233 (1960).

one. However if it is assumed that the quinone moiety does not preexist in liriodenine but is generated along with the carboxyl during the oxidation, then we would have an alternative explanation for the experimental results. The infrared spectrum of liriodenine as compared with benzo[g]quinoline-5,10-dione was in agreement with this idea. The latter compound showed two carbonyl peaks whereas the alkaloid (supposed to have three carbonyl groups) had only one sharp peak. If liriodenine has only one carbonyl then two oxygen functions have still to be accounted for, they cannot be either hydroxyl (no OH in the I.R.) or methoxyl (negative Zeisel). This leaves cyclic ethers as the only possibility and the simplest one which would account for both oxygens is a methylenedioxy group. Support for this hypothesis is to be found in the infrared spectrum[1] of the alkaloid which has bands at 1490, 1420, 1360, 1120, 1050 and 960 cm^{-1}, positions considered to be diagnostic[4] for the methylenedioxy group. With these ideas in mind, and remembering that the tulip tree is in the family Magnoliaceae from which up till now only benzylisoquinoline type bases have been isolated, we arrive at a new possible structure, 1,2-methylenedioxy-7-oxo-dibenzo-[de-g]quinoline(III)[5] for liriodenine.

On this basis then, liriodenine oxime (IV) should show neither hydroxyl nor carbonyl bands in the infrared. The special conditions for the formation of the acid (II),



III



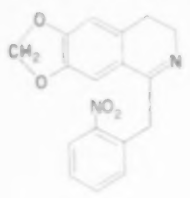
IV

which is known[6] and with which its properties are in good agreement, are now clear. Liriodenine is stated to give reactions characteristic of quinones. The structure III is consistent with these tests in as much as its reduction products would be expected to reoxidize very easily; compare, for example, the analogous case of perinaphthen-1-one.[7]

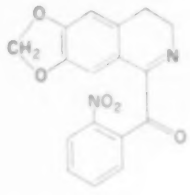
These conclusions received confirmation through a facile synthesis of liriodenine. The route took advantage of the knowledge which had been gained by earlier workers in the preparation of 1-benzoylisoquinolines from 1-benzyl-3,4-dihydroisoquinolines[8] as well as the results obtained from Pschorr cyclizations of 1-2′-aminobenzoyltetrahydroisoquinolines.[9] Thus 1-2′-nitrobenzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline[10] (V) upon oxidation with chromic oxide in acetic acid gave the benzoyl derivative (VI) which in hot alcoholic alkali furnished the desired 1-2′-nitrobenzoyl-6,7-methylenedioxyisoquinoline (VII). Reduction of this compound, diazotization and

[4] L. H. Briggs, L. D. Colebrook, H. M. Fales and W. C. Wildman, *Analyt. Chem.* **29**, 904 (1957).
[5] The unsubstituted heterocycle is known, British Patent 450,244 [*Chem. Abstr.* **30**, 8638 (1936)] but no physical properties are given and the synthetic route, ring closure of 1-benzoylisoquinoline with aluminium chloride, is not applicable to a synthesis of liriodenine.
[6] A. Etienne and A. Staehelin, *Bull. Soc. Chim. Fr.* 748 (1954).
[7] E. Clar, *Aromatische Kohlenwasserstoffe* (2nd. Ed.). Springer, Berlin (1952).
[8] *Inter alia*, J. S. Buck, R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.* **125**, 2176 (1924).
[9] E. Schlittler and A. Lindenmann, *Helv. Chim. Acta* **32**, 1880 (1949).
[10] G. Barger and G. Weitnauer, *Helv. Chim. Acta* **22**, 1036 (1939).

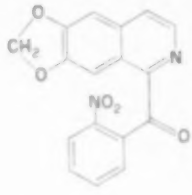
heating to effect the Pschorr cyclization gave directly a product indistinguishable from liriodenine. This synthetic route should prove applicable to other members of this class of alkaloid. For example, Buchanan and Dickey[1] have isolated a second yellow alkaloid which was characterized but no formula was given. From the data



V



VI



VII

presented we believe that it may be a tetramethoxy analogue of liriodenine, perhaps 1,2,9,10- or 1,2,10,11-tetramethoxy-7-oxo-dibenzo[de,g]quinoline. This point is being investigated synthetically.

The yellow bases isolated from the tulip tree may be artefacts produced by aerial oxidation of (nor) aporphines but Buchanan and Dickey have not reported any other alkaloids from the heartwood. On the other hand these yellow bases may be widely distributed albeit in low yield and may have escaped detection until now because so much of the work on the isolation of isoquinoline alkaloids has been carried out before chromatographic methods became widely used.

The occurrence of liriodenine adds one more example to those alkaloids which exist in a higher oxidation state than required by the primary biogenetic process. The function, if any, of liriodenine in the plant is not known, but since it can theoretically accept one electron to form a stable anion radical, its participation in the biological transference of electrons, i.e. in oxidative and reductive processes, is a distinct possibility.

Note added in proof: We have now shown by a synthesis starting from papaverine that the second unnamed yellow alkaloid is 1,2,9,10-tetramethoxy-7-oxodibenzo [de,g]-quinoline and that the aporphine, d-glaucine, is the major alkaloid of the heartwood.

EXPERIMENTAL

1-2′-Nitrobenzoyl-6,7-methylenedioxy-3,4-dihydroisoquinoline (VI)

1-2′-nitrobenzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline[10] (1 g) dissolved in acetic acid (10 ml) was warmed with chromic oxide (1 g) to 60° when a vigorous exothermic reaction set in. The temperature rose to 105° before subsiding. The reaction mixture was diluted with water and the resulting precipitate was extracted into methylenechloride which was then washed with alkali, dried and concentrated. Methanol was added and the remaining methylenechloride boiled off whereupon the product (VI), 450 mg, m.p. 180–183°, crystallized out. (Found: C, 62·8; H, 3·7. $C_{17}H_{12}O_5N_2$ requires: C, 63·0; H, 3·7%).

1-2′-Nitrobenzoyl-6,7-methylenedioxyisoquinoline (VII)

The above benzoylisoquinoline (250 mg) was dissolved in boiling ethanol to which several drops of 50% sodium hydroxide were added. The solution took on a purple color which gradually faded along with the appearance of a crystalline substance. After 10 min further heating the solution was allowed to cool and the pure benzoylisoquinoline (VII), 250 mg, m.p. 252° (decomp.) was filtered off. (Found: C, 63·0; H, 3·4. $C_{17}H_{10}O_5N_2$ requires: C, 63·4; H, 3·1%).

Liriodenine (III)

The above nitro compound (210 mg) was suspended in ethanol and shaken in an atmosphere of hydrogen, using a Raney nickel catalyst (ca. 500 mg) for 16 hr. After filtration, and concentration to dryness, the resulting solid (150 mg) was taken up into methanol (5 ml) and 2 N sulphuric acid (5 ml), cooled to zero degrees and diazotized (0·5 ml of N sodium nitrite were used). The reaction mixture was heated on a steambath for 30 min when it assumed a bright red color. Upon cooling, basifying and extraction into methylenechloride, there was obtained a yellow crystalline residue (100 mg) which gave directly from chloroform a product (40 mg), m.p. 289°, whose ultraviolet and infrared spectra were respectively identical with those recorded for liriodenine. (Found: C, 74·0; H, 3·3. $C_{17}H_9O_3N$ requires: C, 74·2; H, 3·3%).

Acknowledgement—We are indebted to Dr. E. Schlittler for many interesting discussions during the development of this work.

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SYNTHETIC APPLICATIONS OF 1,2-DIHYDROISOQUINOLINES

SYNTHESIS OF (±)-COREXIMINE

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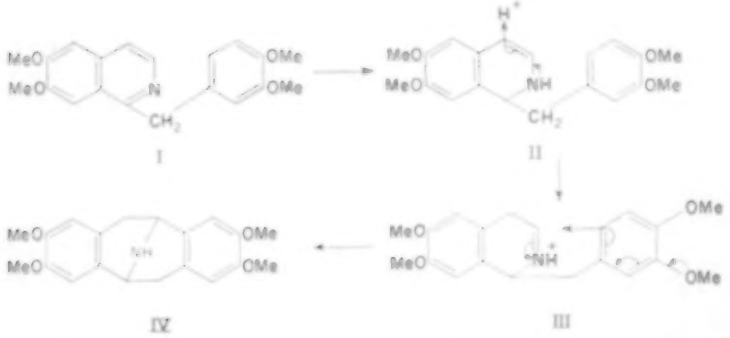
(*Received* 26 *November* 1960)

Abstract—1,2-Dihydroisoquinolines are shown to be useful synthetic intermediates and are employed here for the synthesis of (±)-norcoralydine (XIa) and (±)-coreximine (XIc).

ONE of the products formed during the reduction of papaverine (I) with tin and hydrochloric acid[1] is named pavine and it has been shown[2,3] to have the structure (IV). The formation of this compound is best explained[2,4] by a mechanism which involves protonation of 1,2-dihydropapaverine (II) produced initially by partial reduction of papaverine (I). It is known that enamines take up a proton to give the corresponding imine salts[5] and in this case the resultant salt (III) can cyclize as indicated to afford pavine (IV). The last step in this sequence seemed to be a potentially useful one for many syntheses in the field of isoquinoline alkaloids and its efficacy was demonstrated by the preparation of (±)-norcoralydine (XIa) by this method; a preliminary account



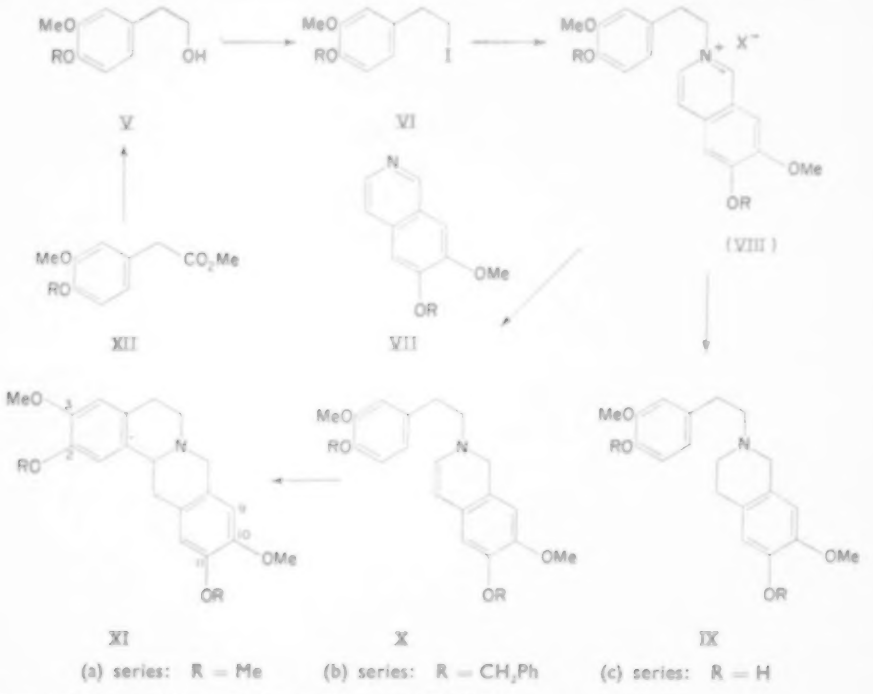
has been published.[6] Concurrently, several valuable syntheses involving 1,2-dihydroisoquinolines were carried out independently in the indole field[7] and there have been more recent applications.[8] The present paper will give a full account of our earlier work together with recent studies leading to the synthesis of (±)-coreximine (XIc).

The preparation of (±)-norcoralydine called for 3,4-dimethoxyphenylethyl iodide (VIa) which was derived from the corresponding alcohol (Va) by the method

[1] F. L. Pyman, *J. Chem. Soc.* **95**, 1610 (1909); F. L. Pyman and W. C. Reynolds, *Ibid.* **97**, 1320 (1910).
[2] A. R. Battersby and R. Binks, *Chem. & Ind.* 1455 (1954); A. R. Battersby and R. Binks, *J. Chem. Soc.* 2888 (1955).
[3] C. Schöpf, *Angew. Chem.* **62**, 453 (1950).
[4] E. Ochiai and K. Harasawa, *Pharm. Bull. Japan* **3**, 369 (1955).
[5] N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.* **76**, 2781 (1954).
[6] A. R. Battersby, R. Binks and P. S. Uzzell, *Chem. & Ind.* 1039 (1955).
[7] K. T. Potts and R. Robinson, *J. Chem. Soc.* 2675 (1955); B. Belleau, *Chem. & Ind.* 229 (1955); *cf.* P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.* **71**, 3207 (1949).
[8] R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 332 (1958); J. W. Huffman, *J. Amer. Chem. Soc.* **80**, 5193 (1958); D. R. Liljegren and K. T. Potts, *Proc. Chem. Soc.* 340 (1960).

using triphenylphosphite methiodide.[9,10] When the iodide (VIa) was heated with the known[11] 6,7-dimethoxyisoquinoline (VIIa), the quaternary salt (VIIIa; $X^- = I^-$) was obtained and attempts were made to reduce this partially to the 1,2-dihydroisoquinoline (Xa) over platinum in the presence of alkali.[12] However, two moles of hydrogen were absorbed without a break in the rate of uptake to yield a crystalline base having the ultra-violet absorption expected for the tetrahydroisoquinoline (IXa). Its structure was confirmed by showing that the same base was formed when the salt (VIIIa; $X^- = Cl^-$) was reduced with borohydride in methanol, a reagent which is known to reduce quaternized isoquinolines smoothly to 1,2,3,4-tetrahydroisoquinolines.[13]

Lithium aluminium hydride in ether has been used to reduce quaternized isoquinolines to 1,2-dihydroisoquinolines,[14] but because of the extremely low solubility of our salts in ether, the reaction was conveniently carried out at room temperature in tetrahydrofuran. Under these conditions, the salt (VIIIa; $X^- = I^-$) gave a high yield of an unstable base (Xa) which had an ultra-violet absorption spectrum corresponding closely with that of 2-methyl-1-phenyl-1,2-dihydroisoquinoline.[16] Our product, without purification or delay, was cyclized by being heated with a mixture of phosphoric and formic acids. Fractionation of the basic products gave (±)-norcoralydine (XIa), identical with an authentic specimen,[15] in 40 per cent overall yield from



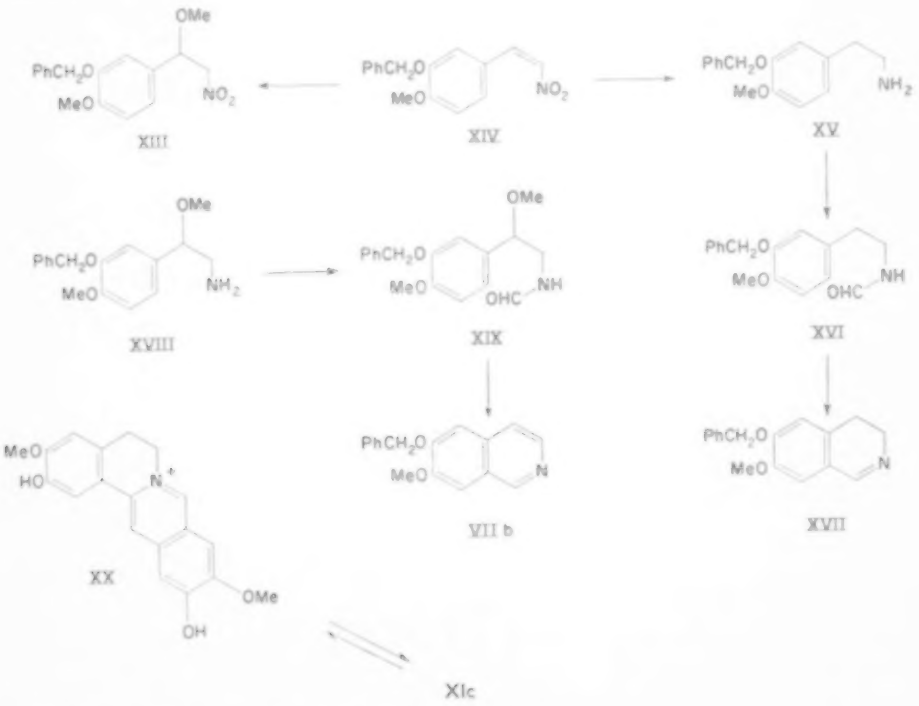
(a) series: R = Me (b) series: R = CH_2Ph (c) series: R = H

[9] S. R. Landauer and H. N. Rydon, *J. Chem. Soc.* 2224 (1953).
[10] *cf.* M. Barash and J. M. Osbond, *J. Chem. Soc.* 2157 (1959) where a different procedure is used.
[11] E. Späth and N. Polgar, *Monatsh.* **51**, 190 (1929).
[12] C. Schöpf, *Experientia* **5**, 201 (1949); C. Schöpf, G. Herbert, R. Rausch and G. Schröder, *Angew. Chem.* **69**, 391 (1957).
[13] R. Mirza, *J. Chem. Soc.* 4400 (1957); S. Cox, B.Sc. Thesis, Bristol (1956).
[14] H. Schmid and P. Karrer, *Helv. Chim. Acta* **32**, 960 (1949).
[15] A. Pictet and T. Q. Chou, *Ber. Dtsch. Chem. Ges.* **49**, 370 (1916).

the salt (VIIIa; $X^- = I^-$). A new route to the protoberberine alkaloids is thus available; the same method was used subsequently in similar work.[16]

In order to extend this procedure to a natural alkaloid, the synthesis of coreximine (XIc) was undertaken. This base, which has not previously been synthesized, occurs in *Dicentra eximia*[17] and until last year was the only protoberberine alkaloid having the 2,3,10,11 oxygenation pattern; all the many other alkaloids in this group carried oxygen functions at positions 2, 3, 9 and 10. However, *Xylopia discreta* (L. FIL.) Sprague and Hutchins has recently yielded xylopinine, which is (−)-norcoralydine (XIa), and discretinine, a closely related alkaloid.[18]

The iodide (VIb) necessary for the coreximine synthesis was readily prepared by the action of triphenyl phosphite methiodide[9] on the corresponding alcohol (Vb), which in turn was obtained by reduction of the ester (XIIb) with lithium aluminium hydride. Synthesis of the isoquinoline (VIIb), however, proved more difficult. The first route involved formylation of the known[19] phenethylamine (XV) by hot formic acid and Bischler–Napieralski ring-closure of the product (XVI) to give the 3,4-dihydroisoquinoline (XVII). These stages ran smoothly and the base (XVII) is now readily available. However, attempted dehydrogenation by several catalytic and chemical methods, under a variety of experimental conditions, failed to yield the desired isoquinoline (VIIb).



[16] J. W. Huffman and E. G. Miller, *J. Org. Chem.* **25**, 90 (1960).
[17] R. H. F. Manske, *Canad. J. Res.* **16B**, 81 (1938).
[18] J. Schmutz, *Helv. Chim. Acta* **42**, 335 (1959).
[19] R. Robinson and S. Sugasawa, *J. Chem. Soc.* 3163 (1931); E. Späth, A. Orechoff and F. Kuffner, *Ber. Dtsch. Chem. Ges.* **67**, 1214 (1934).

The successful route started with the addition of methoxide anion[20] to the nitrostyrene (XIV) to give the methoxynitro derivative (XIII). Lithium aluminium hydride reduction then yielded the oily methoxy amine (XVIII), which was purified as its crystalline picrolonate; the pure base was readily formylated by formic acetic anhydride to afford the amide (XIX). Attempted ring closure of this material under the usual conditions gave a negligible yield of basic material; only after careful study of experimental conditions was it possible to obtain the desired isoquinoline (VIIb). This reacted with the iodide (VIb) in boiling methanol and the resultant salt (VIIIb; $X^- = I^-$) was converted into the corresponding chloride by passage over IRA-400 resin in the chloride phase. Again catalytic hydrogenation of this material was unsatisfactory though the ultra-violet spectrum of the products suggested that some dihydroisoquinoline (Xb) had been formed; the corresponding tetrahydroisoquinoline (IXb) was prepared for comparison purposes from the quaternary salt (VIIIb; $X^- = Cl^-$) by borohydride reduction. Partial reduction of the chloride (VIIIb; $X^- = Cl^-$) was achieved at room temperature as before with lithium aluminium hydride in tetrahydrofuran and the ultra-violet spectrum of the unstable dihydroisoquinoline (Xb) so produced was very similar to that of the tetramethoxy analogue (Xa). Ring-closure of the dihydroisoquinoline (Xb) was carried out without delay in a mixture of phosphoric and formic acids and in this case, concomitant removal of the protecting benzyl groups occurred to yield (±)-coreximine (XIc) directly.

In order to provide a comparison sample, natural (−)-coreximine was dehydrogenated with mercuric acetate to a yellow product. This, by analogy with related cases,[21] is presumably the salt (XX), which without isolation was reduced by zinc and acid to afford (±)-coreximine (XIb). The synthetic material above and the sample prepared from natural coreximine were proved to be identical by melting point and mixed m.p. and their infra-red spectra were superimposable. The ultra-violet spectra of the two samples were identical in neutral and in alkaline solution. So far as we are aware, this represents the first synthesis of a naturally occurring alkaloid in either the isoquinoline or indole series by the 1,2-dihydroisoquinoline route.

Note added in proof: The paper by M. Tomita and J. Kunitomo [*J. Pharm. Soc. Japan* **80**, 1238 (1960)] has now become available to us in which the synthesis of (±)-coreximine by a different route is described.

EXPERIMENTAL

3,4-*Dimethoxyphenethyl iodide* (VIa)

Triphenyl phosphite (10·1 g), methyl iodide (3 ml) and 3,4-dimethoxyphenylethyl alcohol (5·4 g) were heated under reflux for 48 hr, further portions (1 ml) of methyl iodide being added after 4, 14 and 24 hr. The cooled reaction mixture in ether (150 ml) was then washed with 2 N-sodium hydroxide (18 ml) and with water (4 × 10 ml) and after being dried, the ether was evaporated. Distillation of the residue at 114–118°/0·05 mm gave a partially crystalline distillate from which the desired iodide (VIa) (2·4 g) was obtained by careful crystallization and recrystallization from methanol, m.p. 46–48° (Found: C, 41·0; H, 4·8. Calc. for $C_{10}H_{13}O_2I$: C, 41·1; H, 4·45%).

2-(3′,4′-*Dimethoxyphenethyl*)-6,7-*dimethoxyisoquinolinium iodide* (VIIIa; $X^- = I^-$)

A solution of the foregoing iodide (1·0 g) and 6,7-dimethoxyisoquinoline[11] (0·59 g) in methanol (7 ml) was heated under reflux for 8 hr. After the reaction mixture had been cooled, the *isoquinolinium*

[20] *cf.* K. W. Rosenmund, M. Nothnagel and H. Riesenfelt, *Ber. Dtsch. Chem. Ges.* **60**, 392 (1927).
[21] R. H. F. Manske, *J. Amer. Chem. Soc.* **72**, 4796 (1950).

iodide was collected (1·34 g; 89%) and recrystallized from aqueous methanol, m.p. 209–210° (decomp.). (Found: C, 52·2; H, 4·9; N, 2·9. $C_{21}H_{44}O_4NI$ requires: C, 52·4; H, 5·0: N, 2·9%).

2-(3′,4′-*Dimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (IXa)

(a) *By catalytic hydrogenation.* A solution of the foregoing quaternary iodide (0·75 g) in 50% aqueous acetone (500 ml) was passed through a column (8 in. × 0·7 in.) of "Amberlite" IRA-400, chloride phase. The main solution and washings were combined and evaporated to dryness to yield the quaternary chloride (VIIIa; $X^- = Cl^-$).

A portion (20 mg) of this was hydrogenated at room temperature and pressure over Adams' platinum in methanol (10 ml) containing 2 N-aqueous sodium hydroxide (0·3 ml). Hydrogen (2 moles) was absorbed smoothly over 2 hr and the solution was then filtered, diluted with water and freed from methanol by evaporation. Ether extraction of the aqueous suspension then yielded a crystalline base (16 mg) which was recrystallized from ethanol to yield the *tetrahydroisoquinoline* (IXa), m.p. and mixed m.p. with the product from (b), 113–114°.

(b) *Borohydride reduction.* An excess of sodium borohydride (0·2 g) was added portionwise to a solution of the above quaternary chloride (0·13 g) in methanol (10 ml). After being kept at room temperature for 2 hr, the solution was acidified, diluted with water and evaporated until free from methanol. The aqueous solution was then basified and worked up as in (a) to give the tetrahydroisoquinoline (IXa) (0·11 g), m.p. 113–114°. (Found: C, 70·4; H, 7·7. $C_{21}H_{27}O_4N$ requires: C, 70·55; H, 7·6%).

(±)-*Norcoralydine* (XIa)

A suspension of the quaternary iodide (VIIIa; $X^- = I^-$) (0·2 g) in anhydrous tetrahydrofuran (30 ml) was shaken with lithium aluminium hydride (0·2 g) at room temperature for 18 hr. Aqueous 33% (w/v) sodium potassium tartrate was then added carefully until the excess of hydride had been decomposed and a gelatinous precipitate had formed. The clear solution was decanted, the precipitate was washed with tetrahydrofuran (3 × 15 ml) and the combined organic solutions were diluted with water (50 ml). After the tetrahydrofuran had been evaporated under nitrogen, the aqueous suspension was rapidly extracted with ether (3 × 100 ml) and the extracts were evaporated to leave an unstable crystalline residue (qualitative ultra-violet absorption in ethanol, λ_{max} 256, 283, 331 mμ; λ_{min} 245, 270, 295 mμ). This material was dissolved in 5:1 by vol. 98% formic acid:phosphoric acid (12 ml) and heated in an evacuated sealed tube at 80° for 28 hr. The contents of the tube were poured into water (25 ml) and the solution was basified with sodium hydroxide. Ether extraction (3 × 75 ml) as usual gave a largely crystalline base which was fractionated in chloroform on Peter Spence Type "H" alumina to afford (±)-norcoralydine (60 mg), m.p. 157–158° unchanged on admixture with authentic material.[15] The infra-red spectra of the two samples were identical.

3-*Methoxy*-4-*benzyloxyphenethyl alcohol* (Vb)

Methyl 3-methoxy-4-benzyloxyphenylacetate was prepared from vanillin by the known stages of benzylation[22] followed by an azlactone synthesis.[23] In our experiments, the ester crystallized and had m.p. 60–63°.

This ester (5 g) in anhydrous ether (100 ml) was added dropwise over 1 hr to a stirred suspension of lithium aluminium hydride (0·68 g) in ether (100 ml). After the mixture had been heated under reflux for a further 1 hr, it was cooled and the excess of hydride was decomposed with water (5 ml). The ethereal solution was decanted and the inorganic residue was dissolved in hydrochloric acid. This solution was extracted with ether (2 × 50 ml) and the combined ethereal solutions were washed with aqueous potassium hydroxide and water before being dried and evaporated. The crystalline *phenethyl alcohol* (Vb) so obtained (4·0 g) was recrystallized from aqueous methanol, m.p. 70–70·5°. (Found: C, 74·8; H, 7·0. $C_{16}H_{18}O_3$ requires: C, 74·4; H, 7·0%).

3-*Methoxy*-4-*benzyloxyphenethyl iodide* (VIb)

The foregoing alcohol (3·5 g) was reacted with triphenylphosphite (4·7 g) and methyl iodide (1·3 ml) as for the analogue (VIa) above. Distillation of the products at 0·05 mm gave three fractions,

[22] J. Finkelstein, *J. Amer. Chem. Soc.* **73**, 550 (1951).
[23] H. R. Snyder, J. S. Buck and W. S. Ide, *Org. Synth.* **15**, 31 (1935); T. Kametani and J. Serizawa, *J. Pharm. Soc. Japan* **72**, 1081 (1952).

b.p. 135–143°, 143–160°, 160–180° of which the last two crystallized. Recrystallization of these two from aqueous methanol gave the *phenethyl iodide* (VIb) (2·5 g), m.p. 57– 57·7° (Found: C, 51·9; H, 4·7. $C_{17}H_{16}O_2N$ requires: C, 52·2; H, 4·65%).

3-*Benzyloxy*-4-*methoxy*-ω-*nitrostyrene* (XIV)

This material has been prepared previously,[19] but in our hands the ammonium acetate method[24] described below gave the best results.

A solution of 3-benzyloxy-4-methoxybenzaldehyde[19] (258 g) and ammonium acetate (78 g) in glacial acetic acid (770 ml) and nitromethane (128 ml) was heated under reflux for 1¾ hr. The yellow crystals which separated from the cooled solution were collected and washed with ethanol (3 × 10 ml). A second crop was obtained by addition of the acetic acid mother liquor to water (2·5 l) and recrystallization of the gummy precipitate from ethanol (charcoal). The combined crops of crystals were recrystallized from ethanol to give the nitrostyrene (XIV), m.p. 125–127° (200 g), λ_{max} 258, 365 mμ; λ_{min} 230, 286 mμ (log ε 4·0, 4·19, 3·87, 3·45 respectively) in EtOH.

N-(3-*Benzyloxy*-4-*methoxyphenethyl*) *formamide* (XVI)

The foregoing nitrostyrene was reduced by lithium aluminium hydride[25] in tetrahydrofuran to the known[19,25] amine (XI) in 61% yield; our distilled product, b.p. 170°/0·5 mm, crystallized and had m.p. 43–44°.

This amine (20 g) was heated under reflux in a bath at 150° for 5½ hr with formic acid (8·2 g). After the mixture had been cooled, it was dissolved in ethyl acetate (150 ml) and the solution was shaken first with 0.5 N-sodium hydroxide (160 ml), then with N-hydrochloric acid (50 ml) and finally with water. Evaporation of the dried solution left a crystalline residue (22·6 g) which was recrystallized from methanol to yield the pure *formamide* (XVI), m.p. 101°. (Found: C, 71·0; H, 6·6. $C_{17}H_{19}O_3N$ requires: C, 71·55; H, 6·7%).

6-*Benzyloxy*-7-*methoxy*-3,4-*dihydroisoquinoline* (XVII).

A solution of the formamide (XVI) (1 g) in toluene (10 ml) was heated under reflux for 2¾ hr with freshly distilled phosphoryl chloride (5·9 g). The cooled mixture was treated with ice and water (20 g) and when the decomposition was complete, the toluene was shaken with the aqueous layer, separated and back-extracted with water. The combined aqueous solutions were extracted with ether (2 × 50 ml), basified strongly with sodium hydroxide and re-extracted with ether (3 × 50 ml). Evaporation of the combined ethereal solutions left a crystalline residue (0·52 g) which was sublimed in a short-path still to give the *dihydroisoquinoline* (XVII), m.p. 105° (Found: C, 76·7; H, 6·7; N, 5·2. $C_{17}H_{17}O_2N$ requires: C, 76·4; H, 6·4; N, 5·2%). λ_{max} 209, 232, 280, 313 mμ; λ_{min} 220, 250, 296 mμ (log ε 4·29, 4·42, 3·91, 3·85, 4·24, 3·37, 3·71 respectively) in EtOH.

The *picrate* of this base was prepared in methanol and was recrystallized from the same solvent m.p. 188–189° (Found: C, 55·8; H, 4·3; N, 11·0. $C_{23}H_{20}O_9N_4$ requires: C, 55·6; H, 4·1; N, 11·2%).

2-*Methoxy*-2-(3′-*benzyloxy*-4′-*methoxyphenyl*)-*nitroethane* (XIII)

The nitrostyrene (XIV) (14 g) was dissolved in hot anhydrous methanol (1·2 l) and the solution was cooled rapidly to room temperature to produce a fine suspension.[20] 2 N-Sodium methoxide (30 ml) was added and the mixture was shaken for 5 min before the reaction was quenched by the addition of glacial acetic acid (4·0 ml). Evaporation of the solution to dryness under reduced pressure left a gum which was partitioned between ether (250 ml) and water (250 ml). The ether layer was separated and the aqueous solution was extracted with more ether (2 × 250 ml). Evaporation of the dried ethereal solutions left a crystalline residue, m.p. 90·5–92·5° which was suitable for use in the next stage, but which was recrystallized from ether to afford the pure *nitroethane* (XIII), m.p. 102–104° (Found: C, 64·7; H, 6·4. $C_{17}H_{19}O_5N$ requires: C, 64·5; H, 6·1%). λ_{max} 232 (inflexion), 280 mμ; λ_{min} 254 mμ (log ε 3·94, 3·46, 3·05 respectively) in EtOH.

[24] L. C. Raiford and D. E. Fox, *J. Org. Chem.* **9**, 170 (1944).
[25] M. Tomita and T. Nakano, *J. Pharm. Soc. Japan* **72**, 1256 (1952); *Chem. Abstr.* **47**, 12288 (1953).

2-Methoxy-2-(3′-benzyloxy-4′-methoxyphenyl)-ethylamine (XVIII)

A solution of the foregoing nitroethane (10·5 g) in anhydrous ether (160 ml) was added over 30 min to a stirred suspension of lithium aluminium hydride (2·5 g) in ether (200 ml). The mixture was then stirred and heated under reflux for 4 hr. Water (5 ml) was added dropwise to the cooled mixture followed by 6 N-aqueous sodium hydroxide (4 ml) and more water (15 ml). After all reaction had subsided, the mixture was shaken for 15 min, kept for 1 hr, the ether was decanted and the inorganic residue was washed with ether (2 × 200 ml). Evaporation of the dried total ether solution gave a gum (7·9 g) suitable for use in the next stage. It was characterized as the *picrolonate* which was prepared in ethanol and recrystallized from the same solvent, m.p. 183·5–184° (Found: C, 59·1; H, 5·4. $C_{27}H_{29}O_8N_5$ requires: C, 58·8; H, 5·3%).

N-[2-*Methoxy*-2-(3′-*benzyloxy*-4′-*methoxyphenyl*) *ethyl*] *formamide* (XIX)

The crude amine (7·5 g) from the previous experiment was dissolved in formic acid (16 ml) and acetic anhydride (5·2 ml) was added. The solution was then heated at 38° for 45 min, cooled and mixed with ethyl acetate (300 ml). After this solution had been washed with 2 N-hydrochloric acid (2 × 50 ml), 5 N-sodium carbonate (2 × 50 ml), and water (2 × 50 ml), it was dried and evaporated to leave a gum (8·5 g). This, in chloroform (50 ml) was run onto a column of silica gel (200 g) and elution was continued with chloroform. The *formamide* (XIX) formed a middle crystalline fraction (5·0 g), m.p. 82–83° raised to 85° by recrystallization from ether (Found: C, 68·4; H, 6·9. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·7%). ν_{max} 3315 cm^{-1}, 1666 cm^{-1} (NH.CO).

6-Benzyloxy-7-methoxyisoquinoline (VIIb)

A solution of the foregoing amide (0·25 g) in anhydrous toluene (3 ml) was treated at room temperature with freshly distilled phosphoryl chloride (2 ml). The mixture was then slowly heated to the b.p. over 1½ hr and then under reflux for a further 1½ hr. In all, ten such experiments were carried out and they were combined into chloroform (100 ml). Ice-water (80 ml) was added cautiously followed by 2 N-hydrochloric acid (50 ml) and ether (300 ml). After being shaken and separated, the organic layer was washed with 2 N-hydrochloric acid (2 × 30 ml) and water (30 ml). The combined aqueous solutions were basified with potassium carbonate and extracted with ether (3 × 100 ml). Evaporation of the dried ethereal extracts left the crystalline *isoquinoline* (VIIb) which was dissolved in ethanol and treated with picric acid (1·2 equiv.). The precipitated *picrate* was collected and recrystallized from ethanol, m.p. 250° (decomp.) (Found: C, 60·0; H, 3·6. $C_{23}H_{18}O_9N_4$ requires: C, 55·9; H, 3·7%).

A solution of the picrate in the minimum volume of chloroform was passed down a column of alumina (Peter Spence, Type "H") and the colourless percolate was evaporated to yield the isoquinoline (VIIb) (0·6 g), m.p. 127–128°, λ_{max} 206, 236, 265, 312, 324; λ_{min} 214, 262, 302, 318 mμ (log ε 4·25, 4·73, 3·69, 3·46, 3·50, 4·19, 3·68, 3·33, 3·39 respectively) in EtOH.

2-(3′-Methoxy-4′-benzyloxyphenethyl)-6-benzyloxy-7-methoxyisoquinolinium iodide (VIIIb; $X^- = I^-$)

The pure isoquinoline (VIIb) (0·56 g) in methanol (5 ml) was heated under reflux with the iodide (VIb) (1 g) for 24 hr. The crystalline salt (0·73 g), m.p. 203–204°, was collected from the cooled solution and the mother liquor was evaporated to dryness. The residue was partitioned between ether (50 ml) and 2 N-hydrochloric acid (30 ml) and, after separation, the ether layer was extracted with more acid (2 × 30 ml). Basification of the combined aqueous solutions and ether extraction (3 × 50 ml) yielded unchanged isoquinoline (VIIb) (0·21 g). This was treated in methanol (2·5 ml) as before with the iodide (VIb) (0·5 g) to give a further quantity (136 mg) of the salt. The two crops were recrystallized together from methanol to give the *quaternary iodide* (VIIIb; $X^- = I^-$), m.p. 206–207° (Found: C, 61·0; H, 5·3. $C_{33}H_{32}O_4NI.H_2O$ requires C, 60·8; H, 5·3%). λ_{max} 258, 285, 318 λ_{min} 238, 278, 292 mμ (log ε 4·74, 3·76, 4·11, 4·39, 3·76, 3·74 respectively) in EtOH.

2-(3′-Methoxy-4′-benzyloxyphenethyl)-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (IXb)

The iodide (VIIIb; $X^- = I^-$) was converted into the corresponding chloride (VIIIb; $X^- = Cl^-$) by ion-exchange as for the tetramethoxy analogue (VIIIa; $X^- = I^-$) above. Part of this chloride (63 mg) in methanol (10 ml) was reduced with sodium borohydride and worked up as for the tetramethoxy analogue (IXa) to yield the *tetrahydroisoquinoline* (IXb) (45 mg) which was recrystallized

from ether, m.p. 106–107° (Found: C, 77·9; H, 7·2. $C_{23}H_{25}O_4N$ requires C, 77·8; H, 6·9%). λ_{max} 227, 287 λ_{min} 223, 255 (log ε 4·31, 3·87, 4·28, 3·38 respectively) in EtOH.

(±)-*Coreximine* (XIc)

(a) *By synthesis.* Lithium aluminium hydride (0·5 g) was added to a suspension of the quaternary chloride (VIIIb; $X^- = Cl^-$) (0·5 g) in anhydrous tetrahydrofuran (35 ml) and the reactants were shaken at room temperature for 16 hr. The reaction mixture was worked up in the way used in the (±)-norcoralydine experiment above save that the 1,2-dihydroisoquinoline (Xb) was extracted into 3:1 ether–chloroform (3 × 60 ml). Evaporation of the dried extracts left an unstable gum (427 mg) which showed the following qualitative ultra-violet absorption spectrum λ_{max} 255, 280 (inflexion), 329 λ_{min} 245, 295 mμ in EtOH. This material was dissolved in 5:1 by vol. 98% formic acid : phosphoric acid (24 ml) and heated in an evacuated sealed tube at 90° for 24 hr. The contents of the tube were then poured into water (60 ml), the solution was adjusted to pH 9 with sodium carbonate, and then extracted with 3:1 ether–chloroform (3 × 100 ml). Evaporation of the dried extracts left a gum which crystallized on the addition of a few drops of methanol. Recrystallization of the solid from ethanol yielded (±)-*coreximine* (XIc) as colourless prisms (40 mg), m.p. 233–234° alone or on admixture with the material prepared from natural (−)-coreximine. (Found: C, 70·1; H, 6·6. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·5%). λ_{max} 205, 223 (inflexion) 287 λ_{min} 253 mμ (log ε 4·84, 4·17, 3·88, 2·89 respectively) in EtOH. This spectrum was shifted by addition of 10 drops of 8 N-sodium hydroxide to 40 ml of solution to λ_{max} 246·5, 304 λ_{min} 272 mμ (log ε 4·16, 4·07, 3·40 respectively).

(b) *From* (−)-*coreximine.* A solution of (−)-coreximine (20 mg) in glacial acetic acid (8 ml) was heated on the steam bath with mercuric acetate (60 mg) for 5½ hr. The yellow solution was then diluted with 2 N-hydrochloric acid (2 ml), zinc dust (15 mg) was added and the mixture was heated until a colourless solution was obtained. Further portions (15 mg) of zinc dust were added from time to time to maintain a steady release of hydrogen. After the solution had been filtered, it was basified to pH 9 with sodium carbonate and extracted with 3:1 ether-chloroform (3 × 80 ml). The residue recovered from the extracts by evaporation was recrystallized from ethanol to yield (±)-coreximine (8 mg), m.p. 230–232°. The infra-red and ultra-violet spectra of this sample were identical with those of the synthetic base prepared under (a).

The two samples of (±)-coreximine were indistinguishable chromatographically on Whatman No. 1 paper in solvent system "C";[25] the spots were developed with diazotized *p*-nitraniline reagent.

Grateful acknowledgement is made to Dr. R. H. F. Manske for a generous gift of (−)-coreximine, to Dr. R. Binks and Messrs. P. S. Uzzell and D. C. Crouch for their help with preliminary experiments, and to the Department of Scientific and Industrial Research for the award of a Research Studentship (to D. J. Le C.).

[25] H. Schmid, J. Kebrle and P. Karrer, *Helv. Chim. Acta* **35**, 1864 (1952).

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THE STRUCTURE OF AJACONINE[1,2]

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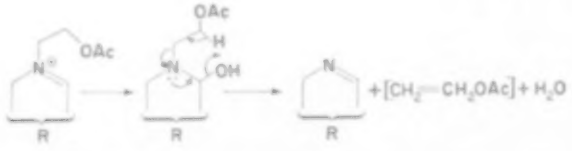
THE alkaloid ajaconine was given its name by Keller and Völker[4] who found it among the bases extracted from *Delphinium ajacis* seeds. Hunter[5] confirmed its presence in this plant and prepared new derivatives. He also recognized its high basic strength. Goodson[6] assigned the correct empirical formula $C_{22}H_{33}O_3N$, and demonstrated the unsaturated character of the base. He was misled into suggesting the presence of an N-methyl group by the products of the Herzig–Meyer determination.

We have obtained the alkaloid from the strong base fraction from *Delphinium ajacis* seeds, and in addition as the major strong base from the seeds of *D. consolida* and a *Delphinium* hybrid. The physical constants, m.p. 167° and $[\alpha]_D$ −122° (*c*, 1·75 in ethanol) correspond closely to those reported by Goodson.[6] Its pK_a' was found to be 11·8 in 50 per cent aqueous methanol, and 11·3 in 80 per cent aqueous ethanol.

The presence of a carbinolamine–ether system N–C–OC in ajaconine was shown[2a] by the fact that it formed immonium salts (ν_{max} 1683 cm^{-1})[7] and that it was reduced by sodium borohydride to a dihydro base without loss of oxygen. The high pK_a' of the base was also consistent with this feature.[7c,8] The presence of three hydroxyl groups in the salts of ajaconine was shown by formation of a triacetyl derivative. The triacetoxy immonium chloride was converted by concentrated aqueous potassium hydroxide at 0°, with immediate extraction into carbon tetrachloride, into a triacetoxy carbinolamine. This base split when gently heated in solution into a small fragment (isolated as acetaldehyde *p*-nitrophenylhydrazone) and a diacetoxy azomethine (ν_{max} 1650 cm^{-1}) analyzing for $C_{24}H_{33}NO_4$. This reaction exactly parallels the fragmentation



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[2] Preliminary communications of some of this work have been published in [c] *Chem. & Ind.* 952 (1957); [b] *Proc. Chem. Soc.* 280 (1958); [c] *Ibid*, 305 (1958).

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[4] O. Keller and O. Völker, *Arch. Pharm.* **251**, 207 (1913).

[5] M. V. Hunter, *Quart. J. Pharm.* **17**, 302 (1944).

[6] J. A. Goodson, *J. Chem. Soc.* 245 (1945).

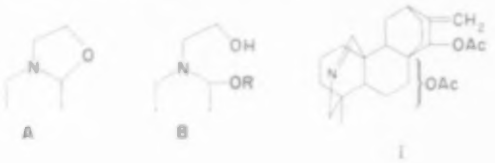
[7a] O. E. Edwards and T. Singh, *Canad. J. Chem.* **32**, 465 (1954); [b] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.* **75**, 4474 (1953); [c] N. J. Leonard and V. W. Gash, *Ibid.* **76**, 2781 (1954).

[8] O. E. Edwards, F. H. Clarke and B. Douglas, *Canad. J. Chem.* **32**, 235 (1954).

of the analogous derivative of atisine, and can be rationalized as above[9] (R = $(CH_3COO)_2C_{18}H_{24}$).

The acetoxy carbinolamines in both cases are soluble in hexane and carbon tetrachloride, hence are non-polar. In view of this and the ease of fragmentation in these solvents, we avoid more ionic forms of reaction mechanism. The presence of the N(β-oxyethyl) system was confirmed by partial synthesis of ajaconine hydrochloride from the azomethine diol obtained by hydrolysis of the above diacetate:

This parallels our earlier partial synthesis of atisine,[9] and completes the evidence for the presence of the systems A or B in ajaconine



This presence of an exocyclic methylene group in ajaconine was evident from the bands near 1665 cm^{-1} and 890 cm^{-1} in the infrared spectrum of ajaconine and its hydrochloride and various degradation products of the alkaloid. When dihydroajaconine was heated with *p*-toluenesulfonic acid in dioxane a product was formed in whose spectrum the above bands had disappeared and carbonyl absorption had appeared at 1705 cm^{-1}. This suggested that the exocyclic methylene was part of an allyl alcohol system in a six-membered or larger ring, which rearranged as shown.[10]

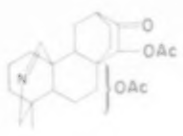
Thus the empirical formula, properties and chemistry of ajaconine were strikingly similar to those of atisine, and the possibility was entertained that ajaconine was a monohydroxyatisine. The identity of the skeletons of the two alkaloids was then proven by degrading ajaconine to a deoxygenated azomethine previously prepared from atisine.[9]

[9] D. Dvornik and O. E. Edwards, *Canad. J. Chem.* **35**, 860 (1957).

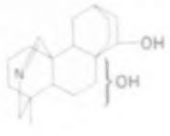
[10] This type of rearrangement was first observed for an atisine derivative by C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.* **170**, 515 (1947); and later by C. Djerassi, A. E. Lippman, S. K. Figdor and J. Herran, *J. Amer. Chem. Soc.* **77**, 4801 (1955) with Garrya alkaloids. See also the model studies of Dreiding and Hartman, *J. Amer. Chem. Soc.* **78**, 1216 (1956).

[11] Since ajaconine proves to have the atisine skeleton, which we now conclude to be correctly represented by I (see below), this will be used for clarity of exposition from this point on. The numbering system used by us[9] conforms with the resin acid numbering and with the biosynthetic postulates for tetracarbocyclic diterpenes of Wenkert [*Chem. & Ind.* 282 (1955)] which have been established as essentially correct by A. J. Birch, R. W. Richards, H. Smith, A. Harris and W. B. Whalley, *Tetrahedron* **7**, 241 (1959).

The above diacetoxyazomethine (I)[11] was oxidized with osmium tetroxide–periodate combination[12] to a ketol diacetate II. Wolff–Kishner reduction of this gave a mixture of the azomethine diol III and the monohydroxy compound IV.[13] Hydrogenation of the mixture over palladium on charcoal converted IV to V. The two components could then be separated by chromatography on alumina. Alternatively, the mixture of III and V arising from the hydrogenation was oxidized with chromic acid. This selectively converted the 8-hydroxyl to a carbonyl. Subsequent Wolff–Kishner reduction left substantially pure V. Sodium dichromate in acetic acid[14] converted V to the ketone VI which was then reduced to VII. This proved identical with the corresponding degradation product from atisine.[9]



II



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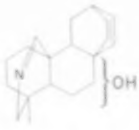
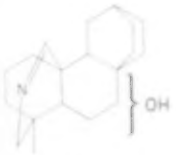
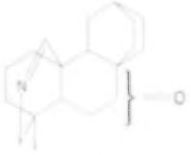


IV



V



VI

VII

The molecular rotation differences for comparable transformations of ajaconine and atisine were nearly identical (Table 1) suggesting that the location and configuration of the substituents on the bicycloöctane system were identical in the two bases.[2a] Fortunately the alkaloid atidine had just been described and the probability that it was a ketodihydroatisine recognized.[15] It seemed to us likely that its carbonyl oxygen and the unknown hydroxyl of ajaconine were on the same carbon. This was quickly proven correct by Pelletier[16], who converted atidine VIII by Wolff–Kishner reduction to dihydroatisine and by borohydride reduction to the dihydroatidine IX. The latter proved identical with the borohydride reduction product of ajaconine. Thus the location of the exocyclic methylene and the location and stereochemistry of the 8-hydroxyl are the same in ajaconine and atisine.

[12] R. Pappo, D. S. Allen, R. U. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956). The course of the osmium tetroxide oxidation of dihydroatisine and dihydroveatchine in which C-16 was oxidized rather than the exocyclic methylene [K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong and J. A. Edwards, *Chem. Ber.* **86**, 800 (1953); S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4144 (1956)] we interpret as involving rapid co-ordination of one mole of osmium tetroxide with the unshared pair of electrons on the nitrogen. The reagent is then in a position to remove the proton on C-16 with the unshared pair on the nitrogen to give an immonium ion, but due to the large steric requirements of the complex does not appreciably attack the otherwise readily accessible exocyclic methylene group. In our experiments the unshared pair of electrons on the nitrogen was unavailable because of prior salt formation.

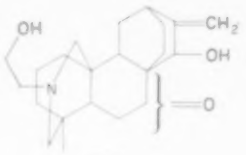
[13] The formation of olefins on Wolff–Kishner reduction of α-ketols has been thoroughly studied by R. B. Turner, R. Anliker, R. Hebling, J. Meier and H. Heusser, *Helv. Chim. Acta* **38**, 411 (1955). The olefin was isolated during the parallel work on atisine.[9]

[14] H. Heymann and L. F. Fieser, *J. Amer. Chem. Soc.* **73**, 5252 (1951).

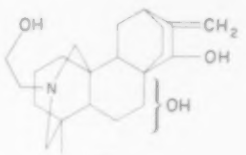
[15] S. W. Pelletier, *Chem. & Ind.* 1016 (1956).

[16] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).

The extra oxygen of ajaconine thus presented the possibility of further testing of the postulated structure for atisine.[17] Hence there was double incentive for locating it and studying its environment. In order to do this we used a derivative containing no functional groups but the nitrogen and the undefined oxygen.

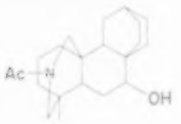


VIII

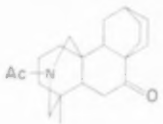


IX

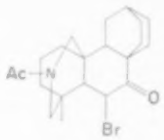
The azomethine alcohol V was reduced with sodium borohydride to the secondary-amino alcohol. This was acetylated and partially hydrolyzed to X. Sodium dichromate in acetic acid oxidized X to the corresponding ketone XI. When brominated in acetic acid in the presence of hydrogen bromide the ketone took up cleanly one mole of bromine to give the monobromo compound XII. The location of the substituents was



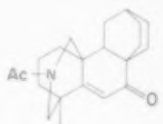
X



XI



XII



XIII

unequivocally shown by elimination of hydrogen bromide from XII to give the α–β unsaturated ketone XIII. The ultraviolet spectrum of XIII (λ_{max} 250 mμ) and the fact that its NMR spectrum contained a sharp one-hydrogen signal in the vinyl hydrogen region are consistent with it being a $\beta\beta$-disubstituted α–β unsaturated ketone with an exocyclic double bond.[18] Three one-hydrogen multiplets between 5·5 τ and

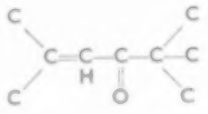
TABLE 1

Ajaconine derivatives	M_D	M_D	Atisine derivatives
C_{20} azomethine diol	−56°	−44°	C_{20} azomethine alcohol
C_{20} diacetoxyazomethine I	−306°	−205°	C_{20} acetoxyazomethine
C_{19} azomethine ketol diacetate II	−511°	−481°	C_{19} azomethine ketol acetate
C_{19} azomethine diol III	−128°	−139°	C_{19} azomethine alcohol
C_{19} azomethine alcohol V	−86°	−84°	C_{19} azomethine

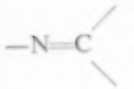
[17] K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954). We considered that selenium dehydrogenation of a bridged skeleton at 340° could have rearranged a related skeleton into the observed phenanthrenes.

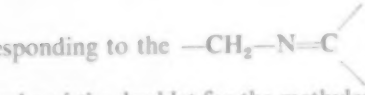
[18] L. F. Fieser and M. Fieser, *Steroids* p. 19. Reinhold, New York (1959).

7·5 τ are very probably attributable to three of the four protons α to the nitrogen.[19] The remaining proton signal appears to be under the methyl band of the acetyl group. If this is correct, it substantiates the evidence from bromination that there is no hydrogen on the other carbon flanking the carbonyl. Hence we can write the environment of the ketone in XIII as



At this point it is desirable to survey the recent evidence bearing on the atisine-ajaconine skeleton. A reaction to be described below proves that C–17 is primary, and hence that the nitrogen is flanked by two such groups. In agreement with this, the N.M.R. spectrum of VII had an unsplit one-hydrogen signal at 2·3 τ corresponding to



(half-band width 7·4 cps) and a two-hydrogen doublet at 7·5 τ (separation 2·4 cps) corresponding to the  hydrogens. The broad azomethine hydrogen signal and the doublet for the methylene are probably caused by long range coupling. However these features prevent a positive conclusion that both carbons α to the nitrogen are attached to quaternary carbons. The methyl signal (9·17 τ) in this and other atisine and ajaconine derivatives is sharp, hence this group can definitely be placed on a quaternary carbon. The infrared spectra of the lactams oxoisoatisine[7a] and three described below, and the spectrum of a lactone derived from the hetero ring[20] showed that the smallest ring incorporating the nitrogen was at least six-membered. These facts are all reconcilable with Wiesner and colleagues' formulation of ring A and the hetero bridge. Indeed it is difficult to reconcile these and the dehydrogenations to 1-methyl-6-ethylphenanthrene[21] and 1-methyl-6-ethyl-3-azaphenanthrene[22] on any other basis.[23] By stepwise degradation of atisine followed by mild aromatization we had converted the bridged system carrying the allyl alcohol into a compound containing the 3,4 disubstituted phenol group XIV.[24] This proved unambiguously the presence

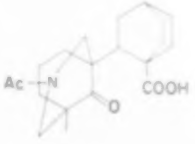
[18] Secondary and tertiary hydrogen attached to carbons adjacent to amide nitrogen and ketone carbonyls absorb in this range. See G.V.D. Tiers, Exploratory N.M.R. studies, Project 737602, Minnesota Mining and Manufacturing Co., St. Paul, Minn., U.S.A.

[19] O. E. Edwards and R. Howe, *Proc. Chem. Soc.* 62 (1959).

[21] W. A. Jacobs, *J. Org. Chem.* **16**, 1593 (1951).

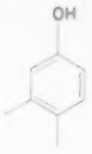
[22] D. M. Locke and S. W. Pelletier, *J. Amer. Chem. Soc.* **81**, 2246 (1959).

[23] We had hoped to provide direct evidence about the size of ring A by oxidation of the α-β unsaturated ketone XIII to the keto acid illustrated. The amorphous acid contained an extra oxygen however, and the attempt was abandoned.

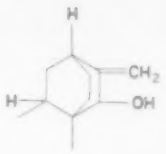


[24] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 623 (1958).

and substitution of the bicycloöctane system to be as shown in XV. If the quaternary



XIV

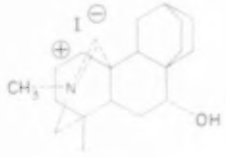


XV

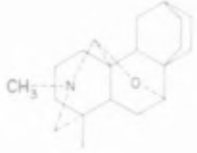
carbon adjacent to the carbonyl in XIII is the quaternary carbon of the bicycloöctane system, then the environment of the ketone fits perfectly the suggested atisine structure.

Thus despite the lack of rigorous proof, in view of the above evidence we now accept with confidence the suggested[17] atisine skeleton, and hence locate the extra oxygen of ajaconine on C–9. The evidence to be presented below unequivocally establishes the relative stereochemistry and fine structure of ajaconine. It also supports the absolute stereochemistry previously suggested for atisine.[24] In the subsequent exposition this absolute stereochemistry will be assumed for clarity.

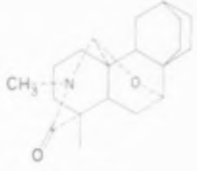
The configuration of the 9-oxygen was established as follows. Methyl iodide converted the azomethine alcohol V to the methiodide XVI. The base liberated from the salt by alkali proved to have no hydroxyl, and analysed correctly for the carbinolamine-ether XVII. Oxidation with permanganate converted this base to a lactam still containing the carbinolamine-ether bridge. Since in no case has it been possible to oxidize C–17 to a carbonyl with external reagents (see below) the lactam must be XVIII and the oxygen links C–9 and C–17. Thus the hydroxyl of V and hence the 9-oxygen of ajaconine is "*cis*" to the hetero bridge.



XVI

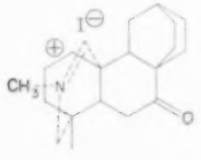


XVII

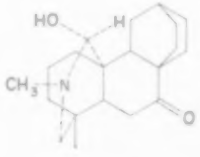


XVIII

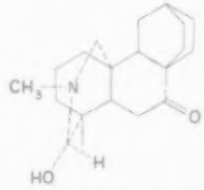
We next consider a unique internal hydride transfer reaction, which gave valuable information about ajaconine.[2b] The azomethine ketone VI was converted to the N-methyl immonium iodide XIX. This proved to be the salt of a very strong base, the carbinolamine XX (pK'_a 11·7). When XX was heated with sodium hydroxide in methanol two reactions took place. One was the isomerization to the isocarbinolamine



XIX



XX

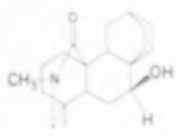


XXI

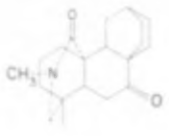
XXI, analogous to the isomerization of atisine to isoatisine. Base XXI had the weaker basicity (pK'_a 9·7) and shift of immonium ion absorption of its hydriodide (1702 cm^{-1} compared to 1688 cm^{-1} for XIX) characteristic of the iso-oxazolidines and carbinolamines.[9]

The second reaction produced an amide, which in view of its inertness to alkali at 200° was a lactam. Its structure was proven to be that shown in XXII in the following way. The hydroxyl configuration was "*trans*" to the hetero bridge since borohydride reduction of the ketone XXIII derived from it gave a high yield of the epimeric alcohol XXIV. Since borohydride reduction of 9-carbonyls in ajaconine derivatives such as VI and in atidine[16] gave back the original α-oriented hydroxyl[25] as major product, XXII must have a β-hydroxyl.

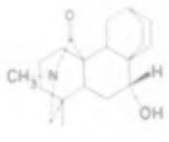
The location of the lactam carbonyl follows from the following evidence, Ketone XXIII was reduced by the Wolff–Kishner method. A lactam was produced which



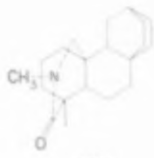
XXII



XXIII

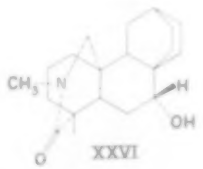


XXIV



XXV

proved different from XXV (prepared by oxidation of the corresponding tertiary amine from atisine).[26] Finally, the methiodide of base V was reduced with sodium borohydride. The acetate of the resulting tertiary-amino alcohol was oxidized to the lactam with Sarret's reagent.[27] Vigorous hydrolysis of the product gave the hydroxy lactam XXVI. This proved different from either of the epimeric hydroxylactams XXII and XXIV, thus the lactam carbonyl of XXII must be on C–17.



XXVI

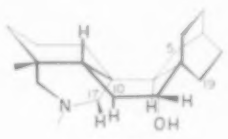
That XXII was formed by internal hydride transfer seemed likely because of the absence of any keto-lactam or carbinolamine–alcohol among the products. Experience with other diterpenoid alkaloids of the atisine[28] and Garrya[13] groups has been that even when C–17 was at an aldehyde oxidation level, oxidation to the 17-oxo compounds is extremely difficult. This is readily rationalized since the 17-hydrogen "*cis*" to the bicycloöctane system is inaccessible to external reagents. Similarly, the 9α-hydrogen of XXII could easily have been transferred from C–17, but is unlikely to have come from an external reagent since the α face of the carbonyl is hindered.

We thus conclude that XXII is formed by internal oxidation–reduction. The mechanism of its formation is discussed further below. Aside from the intrinsic interest

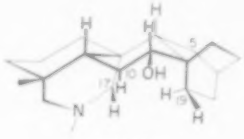
[25] We use α and β to designate orientation below and above the plane of projection respectively.
[26] We are grateful to Dr. R. Howe who carried out this experiment.
[27] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarret, *J. Amer. Chem. Soc.* **75**, 422 (1953).
[28] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **76**, 4496 (1954).

in the new type of hydride transfer reaction[29] these observations gave the first proof that C–17 in the atisine and garryine groups of alkaloids was primary.

With the skeleton and location of the substituents on a firm basis, it is possible to discuss the stereochemistry of ajaconine with confidence. The A : B fusion was proven by the formation of XVII, since the 9 : 17 oxide could not form in the *cis*-fused alternative. An anti coupling of rings A and C follows from the fact that the 9-hydroxyl in its original α-configuration is equatorial. The evidence for this is the high frequency of the C–O stretching absorption in XXIV (doublet at 1077 and 1082 cm^{-1}) and other 9-hydroxy compounds contrasted with the corresponding band at 1054 cm^{-1} in the β-hydroxy compound XXII. In addition the C–O stretching band of the acetoxy group in the acetate of X was a single sharp band at 1236 cm^{-1}.[30] A 9α-hydroxyl on a *trans–syn* skeleton would have to be axial as in XXVII since ring B would have to have a boat conformation, while on the *trans–anti* skeleton with ring B in a chair conformation (XXVIII) it would be equatorial as required.



XXVII



XXVIII

Two lines of evidence confirm this conclusion. The arguments advanced earlier[9] for the origin of the extremely high basic strength of atisine, based on the repulsive interaction of the 10:17:19 hydrogens when C–17 is tetrahedral, and the oxazolidine oxygen: C–5 hydrogen repulsion[31] are only valid if the skeleton is *trans–anti* fused. In the syn skeleton as in XXVII carbons 5 and 19 are remote from carbons 10 and 17. Secondly, the inertness of C–17 to external oxidizing agents discussed above cannot be accounted for on the basis of the *trans–syn* fusion.

With the *trans–anti* fusion proven[32] the arguments put forward[24] for the location of the ally alcohol system on the branch of the bicycloöctane "*trans*" to the hetero bridge are validated.

We are now in a position to consider the fine structure of ajaconine. Dihydroatisine XXIXa and dihydroajaconine XXIXb have comparable moderate rotations (M_D −154° and −150° respectively) hence the 9α hydroxyl contributes little to the rotation. Similarly the oxazolidine atisine XXX has M_D −72°. However all the compounds having a 9:17 carbinolamine-ether have large rotations.[33] Compound

[29] See N. C. Deno, H. J. Peterson and G. S. Saines, *Chem. Rev.* **60**, 7 (1960).

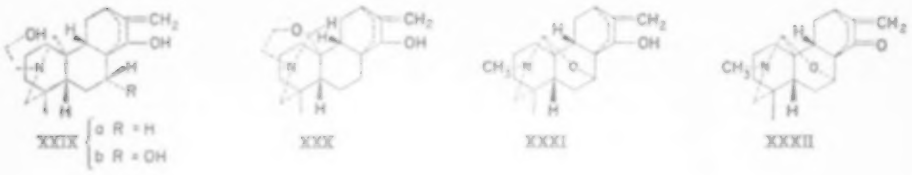
[30] R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **73**, 3215 (1951); A. R. H. Cole, R. N. Jones and K. Dobriner, *Ibid.* **74**, 4571 (1952). The C—O stretching frequency of the alcohols is higher than normal, perhaps because of the extra rigidity of the bridged skeleton.

[31] N. J. Leonard, K. Conrow and R. R. Sauer, *J. Amer. Chem. Soc.* **80**, 5185 (1958) were the first to specify the 5-hydrogen vs. oxazolidine–oxygen interaction as a contributory factor to the anomalous basic strength of atisine. We simultaneously emphasized its importance as the driving force for the atisine to isoatisine conversion.[24]

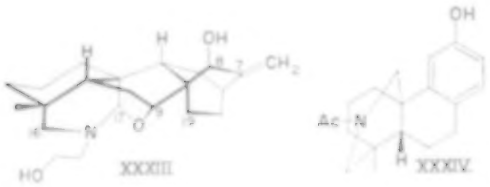
[32] J. Solo and S. W. Pelletier, *Chem. & Ind.* 1108 (1960) have recently presented similar arguments for the *trans–anti* stereochemistry based on our ajaconine work. We had earlier[20,c] shown that the chemistry could be readily accounted for with this sterochemistry, but refrained from positive statement until the basic skeleton was more firmly established.

[33] The large rotational change is probably a result of the change in molecular shape as ring B changes from a chair to boat conformation. However the oxygen on C-17 in a configuration hitherto unknown for atisine derivatives might make a large rotatory contribution.

XVII had M_D −651°, and XXXI and the corresponding α-β unsaturated ketone XXXII had M_D −438° and −336° respectively. Since ajaconine has a rotation identical with that of XXXI (M_D − 439°) we conclude that it is not an oxazolidine but



is instead a 9:17 carbinolamine ether. Thus, in agreement with our earlier tentative assignment,[2r] ajaconine must be represented by XXXIII, with only the 8-hydroxyl configuration uncertain.



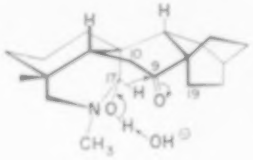
The absolute stereochemistry suggested for atisine[26] was based on the magnitude and sign of rotation of the phenol XXXIV (M_D −314°) derived from it, compared with the rotation of ferruginol (M_D +117°), methyl 6-hydroxydehydroabietate (M_D +234°) and podocarpic acid (M_{Hg} +396°). Support for this assignment comes from the occurrence of ajaconine in *Delphinium* species with the more complex diterpenoid alkaloid lycoctonine, for which the same absolute stereochemistry has been assigned using X-ray crystallography.[34] In addition the ketone XI has an O.R.D. curve with the first extremum (λ 308 mμ, α = +813°) of opposite sign and similar intensity to that of 7-ketocholestane,[35] and the ΔM_D on acetylation of alcohol X is of similar magnitude (−65°) and opposite sign to that for acetylation of 7β-hydroxycholestane (+36°).[36]

The ready formation of the oxide rings in ajaconine and in XVII requires that the boat conformation of ring B have similar energy to the chair conformation. This can only be true if C(17) or C(9) or both are trigonal, so that the bowsprit interactions are eliminated. Of course the bridging by oxygen serves the same purpose. We note that in the boat conformation of ring B the 10:17 interaction disappears, and the 17:19 interaction is reduced, facilitating approach to a transition state involving this conformation. A number of reactions of ajaconine derivatives which illustrate this further will now be described.

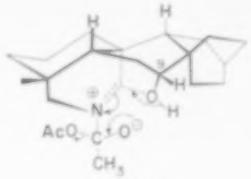
The internal hydride transfer reaction described above requires that ring B be a

[34] M. Przybylska and L. Marion, *Canad. J. Chem.* 37, 1843 (1959).
[35] C. Djerassi, *Optical Rotatory Dispersion* p. 51. McGraw-Hill, New York (1960). We cordially thank Dr. A. K. Bose for determining the O.R.D. spectrum
[36] Ref. 18, p. 253.

boat in the transition state, as illustrated in XXXV. Here the trigonal state of C-9 lowers the energy of the boat conformation.

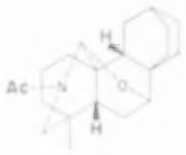


XXXV



XXXVI

A second illustration of the importance of the boat conformation of ring B in influencing the reactions of ajaconine derivatives comes from the acetylation of the azomethine alcohol V. The hydroxyl is predominantly equatorial in the ground state, as shown by the I.R. absorption cited above, and as expected is readily acetylated in most derivatives. Despite this V reacts readily at room temperature with acetic anhydride to give approximately equal quantities of the N-acetyl ether XXXVII and of the normal acetate. We consider that an acetic anhydride molecule approaching V co-ordinates with the unshared pair on nitrogen preferentially. Enough molecules have a boat conformation of ring B that the oxide formation (cf. XXXVI) competes with transfer of the acyl group to oxygen in the normal base-catalyzed esterification process, giving XXXVII.



XXXVII

Finally, the bromoketone XII has its ring B in a boat conformation in the ground state.[2b] This follows from the fact that the bromine is axial (infrared maximum normal at 1702 cm^{-1},[37] but U.V. maximum displaced[38] to 328 mμ). An axial 10α-bromo compound with ring B a chair is impossible, since even a hydrogen in that location is crowded (see above). Hence the bromine must be *trans* to the hetero bridge, and since it is axial ring B must be a boat[39] as illustrated in XXXVIII.

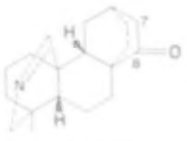
The bromoketone is the product of bromination under thermodynamic control.[39b,40] (HBr catalyst in acetic acid). If the hydrogen bromide is omitted the uptake of bromine is two moles. The reason for this behavior seems to be the bad steric situation of a second bromine replacing the 10-hydrogen in XL due to the 1,3 interaction with the methyl group. This must raise the oxidation potential of the dibromo

[37] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952).
[38] R. C. Cookson, *J. Chem. Soc.* 282 (1954).
[39] Other examples of bromocyclohexanones in boat conformation have been reported. *cf.* [a] C. Djerassi, N. Finch and R. Mauli, *J. Amer. Chem. Soc.* **81**, 4997 (1959); [b] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.* 2907 (1957).
[40] E. J. Corey. *Experientia* **9**, 329 (1953).

compound to the point where it oxidizes HBr when this is in high enough concentration relative to the bromine present.

The bromine of the monobromoketone is under considerable compression from the three axial hydrogens and the one branch of the bicycloöctane system. This and the true *cis* relation of the ajacent hydrogen must be the cause of the very facile pyrolysis of the compound. When the amorphous bromocompound was heated for 2 hr at 100° in vacuo it was transformed in good yield to the hydrobromide of the α–β unsaturated ketone XIII. This proves to be the best way to prepare the latter, since the lithium chloride in dimethylformamide dehydrobromination[41] procedure gave as much as 60 per cent of an intriguing side reaction described below. Unfortunately, the sensitivity of the bromocompound made its use in the determination of the absolute configuration of ajaconine by application of the octant rule hazardous.

The major byproduct of the lithium chloride catalyzed dehydrobromination of XII was a base analyzing correctly for $C_{19}H_{27}ON$, showing no evidence of conjugation in its ultraviolet absorption, and having ν_{max} 1696 cm^{-1} (isolated ketone). The most likely structure seemed to be XXXIX. This was proven correct by reduction of the α-aminoketone system with zinc and acetic anhydride, the product being the N-acetyl ketone XI. (It is interesting to note that an N:C–10 bridge has been postulated for hypognavin by Sakai[42].) Since the unshared electron pair on the amide nitrogen is



XXXVIII

normally not available due to the amide resonance, we consider that the process is most likely a concerted one with chloride ions or a lithium chloride molecule attracted to the amide dipole releasing the nitrogen electrons for the SN_2 displacement.

As expected from the exposed nature of the unshared pair on the nitrogen of XXXIX it reacted rapidly with methyl iodide. The amorphous base produced by the action of sodium methoxide in methanol on this methiodide contained none of the expected α–β unsaturated ketone according to the infrared spectrum.

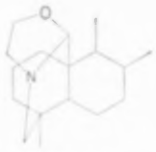
Atisine and ajaconine derivatives present a unique opportunity for the study of the effect of distant polar functions on the basic strength of nitrogen. For example, carbonyls on C–8 and C–9 reduce the basicity of the nitrogen in XL and VI by 0·75 and 1·0 pK_a' units relative to the azomethine VII, respectively. The case of XL represents interaction at a distance of near 5·5 A. We hope to correlate data from these and the more complex diterpenoid alkaloids in a later paper.

In recent years there has been much interest in *trans*-spatial effects on ultraviolet spectra.[43] Two noteworthy examples were found in this work. The long wavelength carbonyl bands of XL[9] and XXIII had intensities of 101 and 99 respectively, three to

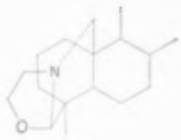
[41] R. P. Holysz, *J. Amer. Chem. Soc.* **75**, 4432 (1953).
[42] S. Sakai, *Chem. & Pharm. Bull.* **7**, 55 (1959).
[43] O. E. Edwards and L. Marion, *Canad. J. Chem.* **32**, 195 (1954); A. Marchant and A. R. Pinder, *J. Chem. Soc.* 327 (1956); E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *Ibid.* 4073 (1956); R. C. Cookson and N. S. Wariyar, *Ibid.* 2302 (1956).

five times that of isolated ketones. These must be effects of the C=N and lactam carbonyl dipoles on the $n \rightarrow \pi^*$ transition probability.

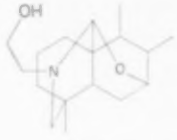
Oxazolidines or carbinolamines with the oxygen on C–17 in the atisine, ajaconine and garrya alkaloid series (type XLI) rearrange on heating with alkali in high yield to the isomeric compounds with the oxygen on C–16 (type XLII). However, attempts to rearrange ajaconine itself gave a mixture, and the N-methyl 9,17-ethers XXXI and XVII failed to isomerize. We hence concluded[2c] that the driving force for the rearrangement is absent in the internal carbinolamine ethers (type XLIII). Inspection of Courtauld models showed that the only major interaction relieved in going from XLI to XLII was that between the 17-oxygen and the nearest hydrogen on C–5. This



XXXIX



XL



XLI

destabilizing factor is absent in the 9:17 ethers. The internal carbinolamine ethers lack the 10:17:19 hydrogen interactions present in XLI and XLII and the interactions of the free hydroxyethyl chain with the ring A hydrogens is probably less than that of the oxazolidines. In addition an entropy factor must favor the internal ether over the oxazolidines. It is thus not surprising that the 9:17 ethers are the more stable of the states represented by XLI to XLIII.

The driving force for the atisine to isoatisine,[44] veatchine to garryine[45] and cauachichicine to isocauachicine[10b] conversions must then, in view of their common stereochemistry,[46] be the above 17-oxygen: 5-hydrogen repulsion.[31,47]

It is interesting that despite the relatively stable character of the internal carbinolamine ethers, the salts of ajaconine and XVII are immonium salts. This would seem to be largely a reflection of the intrinsic stability of the imine and immonium states of nitrogen. For example, there is no evidence for the existence of enamines with secondary nitrogen[48] in the absence of other unsaturation, and tertiary enamines are very strong bases.[49]

Finally, the above structural and stereochemical conclusions relative to atisine and ajaconine confirm the structure and relative stereochemistry assigned to the garrya alkaloids[50] since Pelletier has interrelated the two groups,[32,46] and now enable absolute stereochemistry to be assigned to these also. It is interesting to note that the biosynthetic postulate of Wenkert[11] predicts that the two groups of alkaloids would have the same stereochemistry about their bicycloöctane systems:

[44] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **147**, 567 (1943).
[45] K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Canad. J. Chem.* **30**, 608 (1952).
[46] S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).
[47] *Note added in proof:* We are unable to agree with the recent conformational arguments of Solo and Pelletier [*Proc. Chem. Soc.* 14 (1961)], and consider that the ready rearrangement of XX and one other N-methyl 17-hydroxy compound (unpublished work) to the 16-hydroxy compounds invalidates their explanation of the rearrangement.
[48] B. Witkop, *J. Amer. Chem. Soc.* **76**, 5597 (1954).
[49] R. Adams and J. E. Mahan, *J. Amer. Chem. Soc.* **64**, 2588 (1942).
[50] K. Wiesner and J. A. Edwards, *Experimentia* **15**, 255 (1955).

XLII XLIII XLIV

They would appear then to have a common origin in a diterpene XLIV bearing a mirror image relation to 1-epipimaric acid.[51]

EXPERIMENTAL

Unless otherwise stated ultraviolet absorption spectra were determined in 95% ethanol, infrared spectra as Nujol mulls, and rotations in absolute ethanol. The pK_a' values are the pH's at half titration under the described conditions. Alumina was Woelm brand neutral alumina deactivated where necessary. The cited activities are on the Brockmann scale.[52] Wolff–Kishner reductions were carried out using the Huang-Minlon procedure.[53] Melting points were determined on a Kofler hot stage.

Ajaconine

The bases were extracted by 5% acetic acid[54] from the whole seeds of *D. consolida* and *D. Ajacis*, and from a hybrid which gave a similar alkaloid pattern to that of *D. consolida*. A strong base–weak base separation was effected by adjusting the acid solution to pH 8, extracting with chloroform to remove weaker bases, then making the solution strongly basic (pH > 10) and again extracting with chloroform. The pale yellow strong-base fraction crystallized from concentrated ether solution or from aqueous methanol. The yield of ajaconine was in each case of the order of 0·04%. After recrystallization to a constant melting point of 167° it had $[\alpha]_D$ −122° (C, 1·75), M_D −439°. Its pK_a' in 50% aqueous methanol was 11·8 and in 80% aqueous ethanol 11·3. Its infrared spectrum had bands at 3100, 1665 and 889 cm^{-1} (>C—CH_2); 3380 and 3300 cm^{-1} (OH).

Ajaconine triacetate hydrochloride

A methanol solution of ajaconine was carefully neutralized with a dilute methanol solution of hydrochloric acid. The resulting salt would not crystallize. It was then acetylated by dissolving in acetic anhydride and heating on a water bath for 3 hr. The reagent was removed under reduced pressure. The residue was dissolved in ethyl acetate and again taken to dryness under reduced pressure. When this was repeated using acetone as solvent a foam was produced which was dried at 100° under 1×10^{-3} mm pressure.

(Found: Acetyl 24·30%. Calc. for $C_{28}H_{40}ClNO_6$; 3-acetyl groups, 24·75%).

It had I.R. max at 1735 cm^{-1} (OAc) and at 1667 cm^{-1} (>C—N<$^{\oplus}$) All attempts to crystallize this salt were unsuccessful.

Dihydroajaconine

To a solution of 105 mg (0·292 mmole) of ajaconine in 10 ml of 80% aqueous methanol was added 189 mg of sodium borohydride. After it had been left at room temperature for 1·5 hr the clear solution was evaporated to dryness *in vacuo*, water added and the base extracted with chloroform. Evaporation of the solvent gave a quantitative yield of a white froth, which crystallized as a monohydrate from aqueous acetone, m.p. 99–101°; $[\alpha]_D^{28}$ −39 ± 1° (*c*, 1·04), M_D −150, pK_a' 7·7 (in 90% ethanol titrated with 0·049 N *p*-toluenesulfonic acid in 80% ethanol). The sample for analysis was air-dried at

[51] A. K. Bose, *Chem. & Ind.* 1104 (1960).
[52] H. Brockman and H. Schodder, *Chem. Ber.* **74**, 73 (1941).
[53] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[54] We are indebted to Prof. R. C. Cookson who suggested this technique.

room temperature. (Found: C, 69·60; H, 9·67. Calc. for $C_{22}H_{35}O_3N \cdot H_2O$ (379·52): C, 69·62; H, 9·83%). I.R. max 3350 cm^{-1} (OH); 1795 cm^{-1}, 1652 cm^{-1}, 895 cm^{-1} (>C—CH_2).

Dihydroajaconine triacetate

A solution of 116 mg (0·306 mmole) of dihydroajaconine monohydrate in 10 ml of 1:1 acetic anhydride–pyridine mixture was left for 19 hr at room temperature. The solution was evaporated to dryness under reduced pressure and the residue distributed between ether and an aqueous sodium hydrogen carbonate solution. Evaporation of the solvent left a quantitative yield of a white froth which eventually crystallized from n-pentane. After two recrystallizations from aqueous acetone the product melted at 133–135°; $[\alpha]_D^{20}$ $-92 \pm 2°$ (*c*, 1·11); M_D $-448 \pm 9°$. (Found: C, 69·11; H, 8·35. Calc. for $C_{28}H_{41}O_6N$ (487·62): C, 68·96; H, 8·48). I.R. max 1738, 1728, 1246 cm^{-1} (OAc); 1656 cm^{-1} 893 cm^{-1} (>C—CH_2).

Isomerization of dihydroajaconine

A solution of 41·5 mg (0·11 mmole) of dihydroajaconine monohydrate in 10 ml of dioxane was warmed over refluxing benzene for 14·5 hr with 207 mg (1·2 mmole) of *p*-toluenesulfonic acid in an atmosphere of nitrogen. The solution was evaporated to dryness *in vacuo* and the residue distributed between 3 N aqueous sodium carbonate solution and ether. Evaporation of the solvent left a quantitative yield of a faintly yellow oil, which failed to crystallize. I.R. max (chloroform) 3550 cm^{-1}, 3450 cm^{-1} (OH) 1705 cm^{-1} (six-membered or larger ring ketone).

Diacetoxy C_{20}*-azomethine* I

A solution of 8·96 g of ajaconine in 52 ml of methanol was cooled in an ice bath, then carefully neutralized using 1 N hydrochloric acid. The solution was evaporated to dryness under reduced pressure, giving a white froth. This was dissolved by warming with 45 ml of pyridine, and 45 ml of acetic anhydride added to the solution. After 16·5 hr at room temperature this solution was taken to dryness under reduced pressure. The residue was dissolved in 25 ml of 0·02 N hydrochloric acid, and neutral material removed by two ether extractions. The aqueous layer was then cooled to ca. 5°, emulsified with 20 ml of carbon tetrachloride using a mechanical agitator, and ca. 30 ml of ice-cold 50% potassium hydroxide solution added quickly. After 30 sec the agitation was stopped, the layers separated, and the aqueous layer washed twice with fresh carbon tetrachloride. The combined carbon tetrachloride extracts were dried briefly over anhydrous sodium sulfate, filtered through celite, then slowly concentrated by boiling in an open erlenmeyer flask. After 50 min a concentrated brown solution remained. This was taken to dryness under reduced pressure, sodium carbonate solution added, and the products extracted into ether. The ether solution was extracted twice with 20 cm^3 volumes of 3 N sulfuric acid. The acid solution was back-washed with ether, then the combined ether layers washed with water. When dried and evaporated the ether yielded 530 mg of neutral product which crystallized spontaneously. The acid solution and water wash were made alkaline with sodium carbonate and the liberated base extracted into ether. When evaporated the ether left a yellow, mainly crystalline residue. This was heated with hexane, leaving a reddish brown amorphous residue. The hexane solution contained 8·7 g of crude C_{20} azomethine diacetate. This was adsorbed on 56 g of neutral alumina, activity 1. Hexane, benzene, benzene–ether mixtures and ether eluted 5·9 g (59%) of quite pure diacetate, m.p. 145°. Two recrystallizations from hexane gave a product with m.p. 148° and $[\alpha]_D^{25}$ $-77°$ (*c*, 1·06), M_D $-306°$. A sample sublimed at 147°, 5×10^{-4} mm melted at 152–154°. (Found: C, 72·35; H, 8·48. Calc. for $C_{24}H_{33}O_4N$ (399·51): C, 72·15; H, 8·33%). I.R. max 1737 cm^{-1} (OAc), 1650 cm^{-1} (C=N) and 907 cm^{-1} (>C—CH_2).

In a comparable run using 889 mg of ajaconine the carbon tetrachloride distillate was collected and emulsified with a solution of *p*-nitrophenylhydrazine in 20% solution of acetic acid in water. The precipitate was collected and combined with the solid recovered from the carbon tetrachloride. This was dissolved in chloroform, washed with 3 N hydrochloric acid followed by water. The neutral residue from evaporation of the chloroform was recrystallized from aqueous ethanol giving 167 mg of yellow needles m.p. 115–126°. This was adsorbed on 20 times its weight of neutral alumina, activity 1.

Benzene and 20% ether in benzene eluted 163 mg (38%) of golden yellow solid, which when crystallized from ether–pentane mixture melted at 127–131°. This did not depress the m.p. of authentic acetaldehyde p-nitrophenylhydrazone (m.p. 127–130°).

C_{20}-azomethine diol and its methiodide

A solution of 107 mg (0·268 mmole) of the C_{20}-azomethine diacetate in 10 ml 70% aqueous methanol containing 447 mg of potassium hydroxide was refluxed for 35 min. The clear solution was evaporated to dryness under reduced pressure, water added and the base extracted with chloroform. The residue after removal of solvent was recrystallized from chloroform-n-hexane, giving a quantitative yield (84 mg) of a crystalline product, m.p. 207–209°; $[\alpha]_D^{25}$ −18 ± 1° (*c*, 1·80 in absolute ethanol), M_D −56 ± 3°. The sample for analysis was sublimed at 160–180°/0·5 μ. (Found: C, 76·02; H, 9·16. Calc. for $C_{20}H_{29}O_2N$ (315·44): C, 76·15; H, 9·27%). I.R. max (chloroform) 3570 cm^{-1}, 3400 cm^{-1} (OH); 1650 cm^{-1} (>C=N); 897 cm^{-1} (>C=CH$_2$). The *methiodide* of the base was prepared in 75% yield by reaction with methyl iodide in acetone. m.p. 220° $[\alpha]_D^{25}$ −16°, M_D −71°; pK_a' 10·5 (dissolved in 95% ethanol, titrated with 0·05 N NaOH in 50% aqueous ethanol). I.R. max 1684 cm^{-1} (>C=N$^{\oplus}$<).

Synthetic ajaconine

A solution of 53 mg (0·168 mmole) of the C_{20}-azomethine diol and 0·5 ml of 2-chloroethanol in 4 ml of dimethylformamide was warmed for 24 hr over refluxing benzene. After cooling the solution was evaporated to dryness under reduced pressure, water added, the solution made alkaline and the base extracted with chloroform. Evaporation of the solvent gave 53·5 mg (87% of theory) of a residue which crystallized spontaneously on being sprayed with ether. The product had $[\alpha]_D^{21}$ −117 ± 6° (*c*, 0·65 in abs. ethanol) and showed no melting point depression with a sample of ajaconine.

Diacetoxyazomethine ketone II

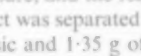
Diacetoxyazomethine I (320 mg, 0·8 mmole) was dissolved in 3·5 ml of 80% aqueous acetic acid. To this was added a solution of 172 mg (0·676 mmole) of osmium tetroxide in 3·5 ml of the same solvent. The solution slowly turned to dark reddish-brown. After one hour at room temperature a solution (heated to dissolve, then cooled) of 571 mg (1·94 mmole) of sodium paraperiodate in 13 ml of 80% acetic acid was added. The color soon began to fade. The solution was left at room temperature for 4 hr at the end of which it was nearly colorless and a crystalline precipitate had formed. The solution was cooled, filtered, and the crystals washed with methanol. The filtrates were taken to dryness under reduced pressure, and the product distributed between chloroform and dilute sodium carbonate solution. The chloroform solution gave 257 mg of white froth. This was adsorbed from benzene onto 2·6 g of neutral alumina, activity 1 (Brockmann). Three 25 ml portions of benzene eluted 187 mg, which after one recrystallization from acetone–ether and two from acetone–hexane melted at 250°. It had $[\alpha]_D^{21}$ −127° (*c*, 1·14). (Found: C, 68·91; H, 7·70. Calc. for $C_{23}H_{31}NO_5$: C, 68·80; H, 7·78%). I.R. max 1755, 1731 cm^{-1} (OAc, C=O) and 1652 cm^{-1} (C=N).

C_{16}-azomethine diol III

The hydrazone was formed from 131 mg (0·326 mmole) of diacetoxyazomethine ketone II using 1·5 ml of 95% hydrazine in 2 ml of triethylene glycol. The solution was heated to 155°, then 1 g of potassium hydroxide added gradually. The bath temperature was raised to 205° and kept there for 4 hr. The reaction mixture was cooled, diluted with water and extracted 3 times with chloroform. The chloroform was back washed 3 times with water. It contained 86 mg of product which crystallized spontaneously. This was adsorbed on 4·3 g of alumina, activity 2. Benzene, ether, and methanol in ether eluted 75 mg. All the fractions when crystallized from acetone gave 39 mg of lovely needles of the azomethine diol III m.p. 225°. The melting point did not change on further recrystallization. It had $[\alpha]_D$ −42° (*c*, 0·95), M_D −128°; I.R. max 3420, 3330, 3160 cm^{-1} (OH), 1657 cm^{-1} (C=N). (Found: C, 75·17; H, 9·20. Calc. for $C_{15}H_{25}NO_2$ (303·43): C, 75·20; H, 9·63%). The mixture of azomethine alcohol, unsaturated azomethine alcohol, and diol in the mother liquors was best treated as described below to obtain pure V.

C_{19}-azomethine alcohol V *and its methiodide*

Crude product from Wolff–Kishner reduction of the diacetoxy azomethine ketone II was hydrogenated over palladium (uptake approximately 20 mole%). The resulting mixture of C_{19}-alcohol and diol (approx. 350 mg) was oxidized overnight with chromium trioxide in acetic acid (1.5 atom equiv of oxygen). The product was reduced by the Wolff–Kishner method, giving 300 mg of product. This was chromatographed on 6·4 g of neutral alumina, activity 2. Forty ml of 50% hexane-benzene eluted 104 mg of quite pure C_{19}-azomethine. Sixty ml of the same solvent and 30 ml of benzene eluted 42 mg of mixture. Benzene and 20% ether in benzene eluted 80 mg of crude C_{19} azomethine alcohol V. The remaining 43 mg of eluate was amorphous.

After recrystallization from acetone-hexane and aqueous acetone V melted at 252°, $[\alpha]_D^{25}$ −30° (*c*, 1·0), M_D −86°. I.R. max 3160, 1084 cm^{-1} (OH), 1659 cm^{-1} (C=N). (Found: C, 79·56; H, 10·05. Calc. for $C_{19}H_{29}ON$ (287·43). C, 79·39; H, 10·17%). The *methiodide* formed readily when methyl iodide was added to an acetone solution of the base. It melted at 275°. (Found: C, 55·78; H, 7·49. Calc. for $C_{20}H_{32}ION$: C, 55·94; H, 7·51%). I.R. max 1672 cm^{-1}  .

Chromic acid oxidation of III (C_{19}-*azomethine ketol*)

To a solution of 128 mg (0·42 mmole of III) in 1 ml of acetic acid was added a solution of 34 mg (0·34 mmole) of chromium trioxide in 2 ml of 90% acetic acid. This was left for 15 hr at room temperature. After addition of around 50 mg of sodium bisulfite the solution was evaporated under reduced pressure. The residue was taken up in 9 ml of 1:1 concentrated ammonia-water, and the product extracted into chloroform. After one recrystallization from acetone–hexane it melted at 211°. Three more crystallizations from the same solvent mixture raised the m.p. to 210–212·5°. I.R. max 3120, 1083, 1075 cm^{-1} (OH), 1723 cm^{-1} (C=O), 1660 cm^{-1} (C=N). (Found : C, 75·98; H, 8·90. Calc. for $C_{19}H_{27}O_2N$ (301·41): C, 75·71; H, 9·03%).

Wolff-Kishner reduction of the C_{19}-azomethine ketol

The hydrazone was formed from the above ketol using 1·5 ml of 95% hydrazine in 1·5 ml of triethylene glycol. After 1 hr at 155°, 1 g of potassium hydroxide was slowly added. The temperature was raised to 200° and maintained there for 4 hr. The solution was cooled, diluted with water and extracted with chloroform. The chloroform was back washed with water. The product (83 mg of white solid) crystallized readily from acetone. It had m.p. 251°, $[\alpha]_D$ −30° (*c*, 1·0), and proved identical in all respects with the C_{19}-azomethine alcohol V.

N-*acetyl carbinolamine-ether* XXVI

The mixture from hydrogenation of the product from Wolff–Kishner reduction of II (see preceding section) (2·28 g) was dissolved in acetic anhydride and left for 20 hr at room temperature. The reagent was removed under reduced pressure, and the residue hydrolyzed by 1½ hr reflux with potassium hydroxide in methanol. The product was separated by distribution between methylene chloride and 3 N sulfuric acid, into 1·08 g of basic and 1·35 g of neutral materials. The base was partially separated by chromatography on a 15-fold ratio of alumina into III and V.

The neutral fraction was adsorbed from benzene onto a 20-fold ratio of alumina of activity 2. Benzene, benzene–ether mixtures and ether eluted 811 mg of XXVI. After recrystallization from pentane this melted at 144°. I.R. max 1647 cm^{-1} (N-acetyl), 1025, 1017 cm^{-1} (ether). (Found: C, 76·73, H, 9·31. Calc. for $C_{21}H_{31}NO_2$: C, 76·55; H, 9·48%).

N-*acetyl carbinolamine ether from* III

A 2% methanol in ether mixture eluted a further 590 mg from the above chromatogram. After four recrystallizations from acetone this melted at 224°. (Found: C, 72·87; H, 8·96. Calc. for $C_{21}H_{31}NO_3$: C, 73·00 H, 9·05%).

Hydrolysis of XXVI

A solution of 537 mg of N-acetyl carbinolamine-ether XXVI in 5 ml of triethylene glycol containing 800 mg of potassium hydroxide and 3 drops of 95% hydrazine was heated in a bath at 195° for 7·5 hr. The product yielded 343 mg of pure starting material and 190 mg of azomethine alcohol V.

After two recrystallizations from acetone and one from methanol-acetone V separated as hexagonal plates, m.p. 252° identical with the sample described above.

C_{19}-azomethine ketone VI *and its methiodide*

To a solution of 83·5 mg (0·29 mmole) of the C_{19}-azomethine alcohol V in 1 ml of glacial acetic acid a solution of 39 mg (0·13 mmole) (34% excess over one atom of oxygen) of finely powdered sodium dichromate dihydrate in 2·5 ml of glacial acetic acid was added. After standing for 65 min at room temperature, the solution was chilled and the excess of the oxidizing agent destroyed by introducing sulfur dioxide. The green solution was evaporated to dryness under reduced pressure and the residue distributed between 10 ml of aqueous ammonia (1:1) and ether. The ethereal solution was washed with 6 N aqueous sulfuric acid and water, and the acidic washings basified. The mixture was then extracted with methylene chloride. Removal of the solvent gave 69 mg (83% of theory) of a n-pentane soluble product, which after being recrystallized from aqueous acetone melted at 123–125·5°; $[\alpha]_D^{25}$ $+5 \pm 1°$ (*c*, 1·15, in absolute ethanol); M_D $+14·5 \pm 3°$. pK_a': 4·3 (in 95% ethanol titrated with 0·05 N *p*-toluene sulfonic acid in 80% ethanol). (Found: C, 79·81; H, 9·36; Calc. for $C_{19}H_{31}ON$ (285·41): C, 79·95; H, 9·54%). I.R. max 1708 cm^{-1} (six or larger ring ketone); 1656 cm^{-1} (>C=N); 1425 cm^{-1} (methylene α to six or larger ring ketone); λ_{max} 245 mμ (log ε 1·94) (C=N), and a shoulder with log ε 1·64 mμ at 280 mμ (>C=O) (95% ethanol).

A crystalline *methiodide*, m.p. greater than 355°, was formed quickly when excess methyl iodide was added to an acetone solution of the base. I.R. max 1706 cm^{-1} (C=O), 1688 cm^{-1} (>C=N⊕): pK_a' 11·7 (95% ethanol solution titrated with 0·05 N sodium hydroxide). (Found: C, 56·29; H, 7·11. Calc. for $C_{20}H_{34}INO$ (427·37): C, 56·20; H, 7·08%).

Wolff–Kishner reduction of the C_{19}-azomethine ketone VI

A solution of 51·5 mg (0·18 mmole) of the C_{19}-azomethine ketone in 1·5 ml of triethylene glycol and 1·0 ml of hydrazine (95%) was immersed in a preheated bath at 110° and the temperature gradually raised to 160°. Approx. 550 mg of potassium hydroxide were added and the mixture heated at $200 \pm 5°$ for 3 hr. After cooling water was added and the mixture extracted with methylene chloride. Evaporation of the solvent gave 36·5 mg (74·5%) of an oil which after being dissolved in n-pentane was adsorbed on a column of neutral aluminum oxide (1:25, activity 1). The material eluted with ether crystallized spontaneously. On recrystallization from aqueous acetone the product melted at 110–112·5°; $[\alpha]_D^{25}$: $-28 \pm 2°$ (*c*, 0·71, in absolute ethanol). The sample for analysis was sublimed at 100° at 0·5 μ. (Found: C, 84·15; H, 10·61. Calc. for $C_{19}H_{29}N$ (271·43): C, 84·07; H, 10·77%). The product was identical with the C_{19}-azomethine base obtained from atisine (mixed m.p. and I.R. spectrum). Its NMR spectrum (60 mc, 22% solution in carbon tetrachloride with 2·5% tetramethylsilane as internal reference) had signals at 2·3τ (half band-width 7·4 cps, one hydrogen) 7·5τ (doublet separated by 2·4 cps, two hydrogens), 9·17τ (sharp, three hydrogens).

Sodium borohydride reduction of the C_{19}-azomethine alcohol V

To a solution of 60 mg (0·21 mmole) of the C_{19}-azomethine alcohol in 7 ml 80% aqueous methanol 100 mg of sodium borohydride was added. After being kept for 1½ hr at room temperature and 15 min on a water bath of 70°C, the solution was evaporated to dryness under reduced pressure. Water was added and the base extracted with methylene chloride. Evaporation of the solvent left 60 mg of the crude dihydro-derivative. After four recrystallizations from acetone–water it melted at 189–190°. $[\alpha]_D^{25}$: $-31 \pm 3°$ (*c*, 0·71), M_D $-90 \pm 5°$. (Found: C, 79·01; H, 10·68. Calc. for $C_{19}H_{31}ON$ (289·45): C, 78·84; H, 10·80%). I.R. max 3140 cm^{-1} (OH); 3350 cm^{-1} (NH).

N-*acetyl* C_{19} *alcohol* X

A solution of 57 mg (0·2 mmole) of the C_{19}-secondary amino alcohol in 10 ml of a mixture of pyridine and acetic anhydride (1:1) was refluxed for 30 min. The residue obtained on evaporation to dryness under reduced pressure was dissolved in ether, filtered from some amorphous precipitate, and washed with 3 N aqueous hydrochloric acid and water respectively. Evaporation of the solvent gave 72 mg (98%) of the crude faintly yellow, oily O,N-diacetate. This was then refluxed for 30 min with

10 ml of 70% aqueous methanol containing 0·5% of potassium hydroxide. The methanol was removed under reduced pressure, water added and the solution extracted with methylene chloride. Removal of the solvent gave 56 mg (87%) of an oily product which crystallized on being sprayed with ether. After being recrystallized from acetone/n-hexane then from aqueous acetone, the product melted at 228°; $[\alpha]_D$ −44 ± 2° (*c*, 0·93); M_D −146 ± 7°. (Found: C, 76·53; H, 9·74. Calc. for $C_{21}H_{33}O_3N$ (331·48): C, 76·09; H, 10·03%). I.R. max 3362 cm^{-1} (OH); 1615 cm^{-1} (amide). A solution of 39 mg of X in 2 ml of triethylene glycol containing 1 g of potassium hydroxide and 2 drops of hydrazine was heated in a bath at 190° for 1 hr. The product consisted of 11 mg of unchanged X (28%) and 26 mg of crystalline secondary amine.

Acetate of X

Pure X was acetylated using 1:1 acetic anhydride-pyridine mixture at 80° for 5 hr. The reagents were removed under reduced pressure. The residue was taken up in methylene chloride and this solution washed with dilute sulfuric acid and sodium carbonate solution. The neutral product melted at 144–146° before and after recrystallization from a hexane-pentane mixture. $[\alpha]_D^{25}$ −57° (*c*, 1·54), M_D −211°. (Found: C, 73·27; H, 9·28. Calc. for $C_{23}H_{35}O_3N$: C, 73·95; H, 9·45%).

N-*acetyl* C_{19} *ketone* XI

To a solution of 32 mg (0·097 mmole) of the N-acetyl C_{19}-alcohol in 1 ml of glacial acetic acid a solution of 12 mg (0·04 mmole) (39% excess over one atom of oxygen) of finely powdered sodium dichromate dihydrate in 4 ml of glacial acetic acid was added. After standing at room temperature for 1 hr, the solution was chilled and the excess of the oxidizing agent destroyed by introducing sulfur dioxide. The green solution was evaporated to dryness under reduced pressure. The residue was distributed between aqueous ammonia (1:1) and ether. Evaporation of the solvent gave 32 mg of a product which after two crystallizations from methylene chloride/n-hexane and one from aqueous acetone had m.p. 188·5–191·5°; $[\alpha]_D^{24}$ −28 ± 1° (*c*, 0·83 in absolute ethanol); M_D −92 ± 3°. (Found: C, 76·63; H, 9·36. Calc. for $C_{21}H_{31}O_3N$ (329·47): C, 76·55; H, 9·48%). I.R. max.: 1698 cm^{-1} (six-membered or larger ring ketone); 1629 cm^{-1} (amide); 1432 cm^{-1} (methylene α to a ketone).

N-*acetyl bromoketone* XII

N-acetyl C_{19}-ketone XI (10·6 mg) was dissolved in 5 ml of a solution of bromine in acetic acid containing hydrogen bromide (stock solution, 94 mg bromine, 0·1 ml of 20% hydrogen bromide in acetic acid, in 20 ml of dry acetic acid). At intervals 1 ml aliquots of the solution were added to aqueous potassium iodide solution and the liberated iodine titrated with 0·02 N sodium thiosulfate. The titre was compared with that corresponding to 1 ml of stock solution determined immediately after each unknown. The molar uptake was 1·0 (2·5 hr), 1·0 (5 hr) and 0·90 (23 hr). In a comparable run without the hydrogen bromide the molar uptake was 1·08 in 3·5 hr and 1·91 in 51 hr.

In a preparative run 56 mg of the N-acetyl ketone was dissolved in 5 ml of stock solution (679 mg of bromine, 0·4 ml of 20% hydrogen bromide in acetic acid in 20 ml of acetic acid).[55] After 17 hr at room temperature in the dark a little solid sodium carbonate was added to neutralize the hydrogen bromide, then the excess bromine and acetic acid were removed under reduced pressure (gentle heating). The residue was dissolved in methylene chloride and dilute sodium carbonate solution. The methylene chloride layer yielded 86 mg of pale yellow bromoketone. This could not be induced to crystallize. (Found: C, 63·63; H, 7·72. Calc. for $C_{21}H_{30}BrNO_3$: C, 61·76; H, 7·40%).

Dehydrobromination of XII

(a) Bromoketone XII (86 mg) was dissolved in 5 ml of dry dimethylformamide and 51 mg of dry lithium chloride added. The mixture was held at 100° for 4 hr, the solvent removed under reduced pressure and the product separated into neutral and basic compounds by distribution between methylene chloride and 6 N sulfuric acid. The 27 mg of neutral product crystallized spontaneously. On recrystallization from acetone–hexane 13 mg m.p. 212° was obtained. The mother liquors gave less pure crystals of the same substance. This proved identical with the α-β unsaturated ketone described below. The 40 mg of base also crystallized spontaneously.

(b) The bromoketone from 60 mg of N-acetyl ketone was dissolved in 6 ml of dimethylformamide and 31 mg of lithium chloride and 60 mg of lithium carbonate added. After 5 hr at 105° the solvent

[55] If more hydrogen bromide was used an oily precipitate formed rapidly.

was removed under reduced pressure and the residue treated as in (a). Forty-five milligrams of neutral product and 16 mg of hexacyclic base were obtained. The neutral fraction crystallized readily giving 29 mg of crude α-β unsaturated ketone.

(c) Amorphous bromoketone XII (48 mg) was maintained at 100° under 0·1 mm pressure for 2 hr. The light brown amorphous product had intense infrared absorption at 1640 cm^{-1} but only a very small peak at 1700 cm^{-1} which might be unchanged bromoketone. By distribution between methylene chloride and 3 N sulfuric acid it was separated in to 43 mg of neutral and 6 mg of basic products. The latter crystallized spontaneously and proved identical with the hexacyclic base described below. The neutral product after one recrystallization melted at 205° and showed no melting point depression with the neutral products from (a) and (b).

N-acetyl α-β unsaturated ketone XIII

The melting point was raised to 211° by chromatography on alumina (25-fold, activity 2), followed by two recrystallizations from acetone; $[\alpha]_D$ +45° (*c*, 0·45); λ_{max} 250 mμ (ε 9300), 329 mμ (ε 96); I.R. max 1664 cm^{-1} (conjugated ketone), 1644 cm^{-1} (amide). (Found: C, 76·88; H, 8·83. Calc. for $C_{21}H_{29}NO_2$ (327·45): C, 77·02; H, 8·93%).

Oxidation of XIII

The α-β unsaturated ketone was inert to osmium tetroxide in ether. A solution of 43 mg of XIII in 5 ml of acetone, 0·05 ml of acetic acid and 0·5 ml of water reduced 50 mg of potassium permanganate in 2 hr, but extra permanganate persisted unchanged. The manganese dioxide was removed by filtration, the acetone evaporated, and the product separated into a trace of acidic material and 54 mg of yellow neutral gum. The latter was dissolved in 10 ml of a saturated solution of lead tetracetate in acetic acid and 1 ml of water, and left for 115 hr at room temperature in the dark. The product was separated into 20 mg of neutral and 21 mg of acid material. The neutral material had lactone character, being opened to an acid in methanolic alkali. This had a different infrared spectrum from the acid produced directly. The latter would not crystallize.

Combined acid fractions from several permanganate-lead tetraacetate oxidation (48 mg) were dissolved in acetic acid (4 ml) and oxidized by shaking for 24 hr with suspended sodium bismuthate (100 mg). After the addition of a drop of phosphoric acid the mixture was filtered and the acetic acid removed under reduced pressure. The product was separated into 6 mg of neutral and 38 mg of acid materials. The latter would not crystallize, but now had a much altered infrared spectrum. The sodium bismuthate oxidation was repeated, 5 mg of neutral product and 26 mg of acid being obtained. The latter had I.R. max 1705, 1745 cm^{-1} (ketone and carboxyl), 1625 cm^{-1} (lactam). Its sodium salt had I.R. max. 1710 cm^{-1} (ketone) and 1635 cm^{-1} (amide). The recovered acid was converted to its methyl ester (CH_2N_2), which was distilled at 150°, 5 $\times$ 10^{-4} mm. (Found: C, 66·54; H, 7·84; Calc. for $C_{21}H_{31}O_3N$: C, 66·82; H, 7·84%).

Hexacyclic base XLI

The crystalline base from the above dehydrobrominations when recrystallized twice from hexane had m.p. 141°, and pK_a' 5·6 (95% ethanol). (Found: C, 80·43; H, 9·49. Calc. for $C_{19}H_{27}NO$: C, 79·95; H, 9·54). Its ultraviolet spectrum had λ_{max} 307 mμ (ε 51) and its infrared spectrum had ν_{max} 1696 cm^{-1} (ketone) but no NH absorption.

A solution of 15 mg of the base in 1 ml of acetic anhydride and 0·5 ml of acetic acid was maintained at 100° for 1·5 hr while a total of 160 mg of zinc dust was added in small portions. The mixture was left overnight at room temperature, then taken to dryness under reduced pressure. The residue was extracted with methylene chloride, and the combined solutions extracted with 6 N sulfuric acid. The 22 mg of neutral material left in the methylene chloride crystallized readily from acetone–hexane giving 16 mg m.p. 191°. This did not depress the melting point of the original N-acetyl ketone XI.

Hexacyclic base methiodide

When 0·25 ml of methyl iodide was added to a solution of 42 mg of the base in 0·5 ml of acetone and 3 ml of ether a precipitate formed nearly instantly. After three hours in the dark the solid was collected, giving 63 mg m.p. 296°. After two recrystallizations from methanol–acetone mixtures its m.p. was 291–293°. (Found: C, 56·49; H, 7·07. Calc. for $C_{20}H_{30}INO$: C, 56·20; H, 7·08%).

Hoffmann degradation of the methiodide (55 mg) by 4 hr heating with potassium hydroxide in aqueous methanol gave 33 mg (92%) of a hexane-soluble oil. The non-crystalline perchlorate of the base had an ultraviolet spectrum having only weak end absorption and a low intensity peak at 275 mμ (carbonyl).

N-methyl carbinolamine ether XXXI

The methiodide of the C_{20}-azomethine diol (220 mg) was dissolved in 5 ml of water, the solution cooled to 0° and 10 ml of methylene chloride added. The two layers were mechanically interdispersed and ice cold 50% potassium hydroxide added. The layers were separated and the aqueous layer extracted twice more with methylene chloride. The organic layers yielded 118 mg of colorless oil (74%). This was dissolved in pentane and filtered from 4 mg of amorphous material. The residual oil had $[\alpha]_D$ −133° (*c*, 1·07). Its pK'_a was 10·6 (in 95% ethanol titrated with 0·05 N *p*-toluenesulfonic acid in 50% ethanol). The oil was distilled *in vacuo*. (Found: C, 76·68; H, 9·48. Calc. for $C_{21}H_{31}O_3N$ (329·47): C, 76·55; H, 9·48%).

Attempted isomerization of XXXI

A solution of 113 mg of the base in 10 ml of methanol containing 0·8 g of potassium hydroxide was refluxed in a nitrogen atmosphere for 3 hr. The recovered oily base had $[\alpha]_D^{26}$ −131° (*c*, 0·9), pK'_a 10·5 (same solvents as above) and its infrared spectrum was identical with the starting material.

α-β unsaturated ketone XXXII

Active manganese dioxide[16] (1·36 g) was suspended for 4·5 hr in a solution of 92 mg of XXXI in ethanol-free chloroform. The solid was removed by filtration. The filtrate and washings contained 73 mg (80%) of crystalline solid. This was recrystallized once from acetone, giving prismatic needles m.p. 146–148°. This was sublimed for analysis. It had $[\alpha]_D^{26}$ −102° (*c*, 0·97), M_D −336°; I.R. max 1706 cm^{-1} (α-β unsaturated ketone), 1635 and 875 cm^{-1} (>C—CH$_2$) and 1044 cm^{-1} (C—O—C); λ'_{max} 222 mμ (ε 6840), 334 mμ (ε 102). (Found: C, 77·29; H, 8·78. Calc. for $C_{21}H_{29}NO_2$ (327·45): C, 77·02; H, 8·93%).

Carbinolamine ether XVII

The methiodide of V (42 mg) was dissolved in 3 ml of hot water, the solution cooled to 10° and cold aqueous potassium hydroxide added. The base was quickly extracted into methylene chloride, giving 27 mg of hexane soluble crystalline product. After one recrystallization from hexane this melted at 155°. It did not depress the melting point of the product from attempted alkali-catalyzed isomerization of the carbinolamine ether (see below).

Attempted isomerization of XVII

The methiodide of V (256 mg) was dissolved in 10 ml of methanol containing 0·49 g of potassium hydroxide. The solution was refluxed for 3 hr under nitrogen. The product was separated into 3 mg of neutral and 160 mg of benzene-extractable base (83%). The base was converted to its hydriodide m.p. 275°. After two recrystallizations from methanol–ethyl acetate it melted at 277°; $[\alpha]_D$ −35° (*c*, 1·04), M_D −150°. (Found: C, 56·36, H, 7·45. Calc. for $C_{20}H_{32}INO$ (429·39): C, 55·94; H, 7·51). I.R. max 3440 cm^{-1} (OH) and 1685 cm^{-1} (>C=N⊕).

The base liberated from this salt was hexane soluble. It crystallized from hexane as prisms, m.p. 155°, $[\alpha]_D$ −216° (*c*, 0·74), M_D −651°. Its infrared spectrum had no bands in the hydroxyl or carbonyl regions. (Found: C, 79·82; H, 10·43; Calc. for $C_{20}H_{31}NO$ (301·46): C, 79·67; H, 10·37%).

Action of alkali on methiodide XIX

A solution of 197 mg of the methiodide and 362 mg of potassium hydroxide in 10 ml of methanol was refluxed under nitrogen for 3 hr. The methanol was removed under reduced pressure, and the product distributed between ether and 6 N sulfuric acid. The base recovered from the acid solutions was neutralized with hydriodic acid in methanol, giving 55 mg of the crystalline hydriodide of XXI.

[16] J. Attenburow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen and T. Walker, *J. Chem. Soc.* 1094 (1952). F. Sondheimer, O. Manura, M. Urquiza and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 4145 (1955).

The ether layers yielded 80 mg of neutral product which crystallized spontaneously. After one recrystallization from acetone 55 mg of pure lactam alcohol XXII was obtained.

Hydriodide of XXI

This crystallized as silky needles from methanol-ethyl acetate mixtures. It melted rather indefinitely around 328°. (Found: C, 56·38; H, 7·09. Calc. for $C_{20}H_{30}ION$ (427·37): C, 56·20; H, 7·08%). I.R. max 3480 cm^{-1} (OH), 1700 cm^{-1} (C—O) and 1685 cm^{-1} ( ).

Lactam alcohol XXII

After recrystallization from acetone–hexane this melted at 244°, $[\alpha]_D$ −4° (*c*, 1·05), M_D −12°. I.R. max 3380, 1054 cm^{-1} (OH) and 1620 cm^{-1}. (Found: C, 75·48; H, 9·70. Calc. for $C_{20}H_{31}NO_2$ (317·46): C, 75·67; H, 9·84%).

Lactam ketone XXIII

A solution of 15 mg (0·050 mmole) of sodium dichromate in 5 ml of acetic acid was added to a solution of 44 mg (0·139 mmole) of lactam alcohol XXII in 2 ml of acetic acid. The mixture was left for 2 hr at room temperature, then excess dichromate reduced with sulfur dioxide. The acetic acid was removed under reduced pressure, and the residue taken up in ether and dilute ammonia solution. The ether extracted 45 mg of colorless oil which was hexane soluble. A filtered hexane solution was taken to dryness and the residue crystallized from pentane. It had m.p. 112°; $[\alpha]_D^{25}$ −3·5° (*c*, 1·73), M_D −11°; I.R. max 1706 cm^{-1} (ketone) and 1650 cm^{-1} (lactam); λ_{max} 280 mμ (ε 99). (Found: C, 76·00; H, 9·16. Calc. for $C_{20}H_{29}NO_2$ (315·44): C, 76·15; H, 9·27%).

α-Hydroxy lactam XXIV

Lactam ketone XXIII (23 mg) was dissolved in 7 ml of 90% aqueous methanol and 26 mg of sodium borohydride added. After 1 hr at room temperature the bulk of the solvent was removed on the steam bath and replaced by water. A crystalline solid separated. Yield 20 mg (85%), m.p. after one recrystallization from acetone–hexane 203°. A mixture of this with the *β*-hydroxy lactam XXII melted between 200 and 215°. It had $[\alpha]_D$ −41° (*c*, 0·66), M_D −130°. I.R. max 3405, 1082, 1077 cm^{-1} (OH), 1620 cm^{-1} (lactam). (Found: C, 75·83; H, 9·68. Calc. for $C_{20}H_{31}NO_2$ (317·46): C, 75·67; H, 9·84%)

Wolff–Kishner reduction of XXIII

Thirty eight mg of lactam ketone XXIII was dissolved in 1·4 ml of triethylene glycol and 1 ml of 95% hydrazine. The solution was heated under reflux in a bath maintained at 150° for 30 min. Potassium hydroxide (0·57 g) was cautiously added, the bath temperature raised to 220° and kept there for 3·5 hr. The reaction mixture was diluted with water and the product extracted into chloroform. The residue from evaporation of the chloroform was dissolved in ether and the solution washed twice with 6 N sulfuric acid and once with water. The ether solution yielded 32 mg of product of which 29 mg was pentane soluble. This was adsorbed from pentane onto 0·6 g of alumina, activity 3. Pentane (150 ml) eluted 22 mg of crystalline solid. This was recrystallized from aqueous acetone giving needles, m.p. 128°. It was sublimed at 125°, 6 × 10^{-4} mm. It had $[\alpha]_D^{25}$ −36° (*c*, 0·61), M_D −108°; I.R. max 1642 cm^{-1} (amide). (Found: C, 79·58; H, 10·24. Calc. for $C_{20}H_{31}NO$ (301·46): 79·67; H, 10·37%).

Hydroxy lactam XXVI

The methiodide prepared from 94 mg (0·327 mmole) of C_{19}-azomethine alcohol V was left for 1 hr with 202 mg of sodium borohydride in 10 ml of 80% aqueous methanol. The 100 mg of oily product was acetylated by 30 min heating at 100° with 10 ml of 1:1 acetic anhydride–pyridine. The product was 112 mg of pale yellow oil with I.R. max (CS_2), 1738 cm^{-1} (OAc). This was left for 15 hr with 324 mg of chromium trioxide in 5 ml of pyridine. The excess oxidizing agent was reduced with sulfur dioxide and the solution then taken to dryness under reduced pressure. Aqueous ammonia was added and the product extracted into ether. The ether layers were washed with 6 N sulfuric acid and water. The ether retained 90 mg (78%) of pentane soluble oil. This was hydrolyzed by refluxing with potassium hydroxide in aqueous methanol. The 72 mg of crystalline neutral product was recrystallized

five times from acetone–hexane. It had m.p. 216·5°, $[\alpha]_D^{24}$ −56° (*c*, 0·57), M_D −178°. A mixture with hydroxy lactam XXIV melted over a wide range starting at 163°. I.R. max 3322, 1090, 1080 cm^{-1} (OH), 1618 cm^{-1} (lactam). (Found: C, 75·78; H, 9·70. Calc. for $C_{20}H_{31}NO_2$ (317·46): C, 75·67; H, 9·84%). The compound was recovered quantitatively after 4 hr refluxing under nitrogen with a 20% solution of potassium hydroxide in 50% aqueous ethanol.

Lactam XXV[26]

The methiodide of VII (from 150 mg of the base) was dissolved in 10 ml of 80% methanol, 130 mg of sodium borohydride added, and the solution left at room temperature for three hours. The solvent was evaporated, dilute sodium carbonate solution added and the product extracted into ether. The 153 mg of product after four recrystallizations from acetone melted at 60° and had $[\alpha]_D$ −71° (*c*, 0.93). (Found: C, 83·74; H, 11·36. Calc. for $C_{20}H_{33}N$: C, 83·56; H, 11·57%).

The above N-methyl base (35 mg) was dissolved in 2 ml of pyridine, and the solution added to a mixture of chromium trioxide (55 mg) and 2 ml of pyridine. After 20 hr at room temperature sulfur dioxide was bubbled into the cooled solution. The pyridine was removed under reduced pressure, dilute hydrochloric acid added, and the neutral product extracted into ether. The ether was washed with water, dried and evaporated. The 22 mg of product crystallized readily. The product from two runs was combined (51 mg) and adsorbed from hexane onto 1·5 g of alumina, grade 4. Thirty milliliters of hexane eluted 31 mg, which after two recrystallizations from pentane had m.p. 136°, $[\alpha]_D$ −57° (*c*, 0·69). I.R. max 1650 cm^{-1} (lactam). (Found: C, 79·91; H, 10·20. Calc. for $C_{20}H_{31}NO$: C, 79·67; H, 10·37%). The lactam was recovered quantitatively after 2 hr at 200° under Wolff-Kishner conditions.

Acknowledgements—We are grateful to Mr. A. Knoll for isolation of the ajaconine and Mr. M. Lesage for its characterization and for valuable technical assistance; to Mr. R. Lauzon for the infrared spectra and Mr. H. Seguin for the microanalyses. We are indebted to Mr. J. Nicolson, Dr. F. A. L. Anet and Dr. H. J. Bernstein for the NMR spectra, and to the latter for advice on interpretation; and to Dr. A. K. Bose for the rotatory dispersion curve.

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RECENT DEVELOPMENTS IN THE CHEMISTRY OF THE ATISINE-TYPE DITERPENE ALKALOIDS

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I. INTRODUCTION

FROM ancient times man has been intrigued and fascinated by powerful plant poisons. Few there are who are not moved by reading Plato's account in the *Phaedo* of Socrates drinking the cup of poison hemlock or the accounts in medieval literature of the use of Monkshood, Ouabain, or Deadly Nightshade in the trials by ordeal. It is perhaps this same kind of fascination which accounts at least in part for the organic chemists' interest in the Aconite[3] alkaloids. These substances occur in the various species of *Aconitum* and *Delphinium*, which are widely distributed throughout the plant world, and have long been of great interest because of their intensely poisonous properties and their complex structures. Extracts of the roots and leaves of *Aconitum* species were employed in ancient times for such varied uses as animal poisons and the treatment of neuralgia, hypertension, gout and rheumatism.

The Aconite alkaloids may be divided into two broad categories. The first comprises the highly toxic ester bases called the Aconitines. These consist of relatively non-toxic, polyhydric C-19 bases (aconines) which are esterified with one or two simple organic acids such as acetic or benzoic acid. The second group which is designated as the "Atisine" class includes a series of relatively non-toxic alkamines containing few substituents and is modeled on a C_{20}-skeleton. It is this second class of "simpler" alkaloids that forms the subject for the present review. Since two recent reviews[4,5] have appeared which cover the literature to about the end of 1957, this survey will be concerned mainly with developments of the past three years, and in particular with only those alkaloids for which complete or at least plausible, if not rigorously demonstrated, structures have been advanced.

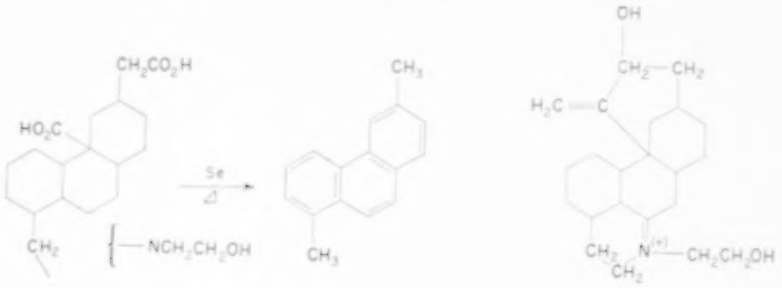
II. THE CHEMISTRY OF ATISINE[6]

A. *General remarks*

Aconitum heterophyllum, Wall (atis or atees), a plant native to the Himalayas, has long occupied an important place in Indian folk medicine. Thus, extracts of the plant have been used as a bitter tonic, expectorant, febrifuge and aphrodisiac, and in the

[1] Fellow of the American-Swiss Foundation for Scientific Exchange, 1960.
[2] The author's investigations of 1959–60, which are reported herein, were supported in part by Grants RG 5807, 5807 (C1) and 5807 (C2) from the National Institutes of Health, United States Public Health Service.
[3] The term "Aconite Alkaloids" was coined by W. A. Jacobs to designate bases of both the *Aconitum* and *Delphinium* species.
[4] K. Wiesner and Z. Valenta, *Progress in the Chemistry of Organic Natural Products* Vol. XVI, p. 26. Springer-Verlag, Vienna (1958).
[5] E. S. Stern in *The Alkaloids, Chemistry and Physiology* (Edited by R. H. F. Manske and H. L. Holmes) Vol. VII, p. 473. Academic Press, New York (1960).
[6] Atisine appears to be identical with anthorine, the alkaloid of *A. anthora* [A. Goris and M. Melin, *C. R. Acad. Sci., Paris* **180**, 968 (1925); A. Goris, *Ibid.* **205**, 1007 (1937)].

treatment of dyspepsia and dysentery. Whether the alkaloids of the plant are responsible for its reputed properties is unknown, but those which have been isolated in a pure state include atisine, atidine, hetisine, heteratisine and a benzoyl derivative of the latter. The predominant alkaloid, atisine, is a clear varnish-like base which was first described and named by Broughton in 1877.[7] Numerous crystalline derivatives were subsequently reported[8–10] but the correct molecular formula ($C_{22}H_{33}NO_2$) remained unknown until the work of Lawson and Topps[11]. The pioneering studies of the Aconite alkaloids by Walter A. Jacobs and his collaborators at the Rockefeller Institute were initiated in 1936 and provided an indispensible foundation for subsequent contributions in this field. Jacobs' work on atisine disclosed the relationship of functional groups and provided deep insight into the complex chemistry of this substance.[12] Unfortunately due to an incorrect assumption that a methyl group in 1,6-dimethylphenanthrene (2) could not have originated from a carboxyl group during dehydrogenation, Jacobs concluded that the dicarboxylic acid from isoatisine must bear an acetic acid residue as in structure (1). This situation, was largely responsible for the postulation of an incorrect skeleton (3) for atisine.[12]



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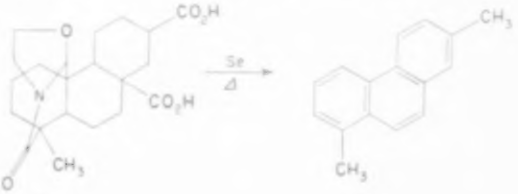
In subsequent work on the Garrya alkaloids,[13] Wiesner paralleled the early studies of Jacobs on atisine and was able to show convincingly that during dehydrogenation one of the carboxyls of oxoveatchine dicarboxylic acid-B (4) is in fact a precursor of a



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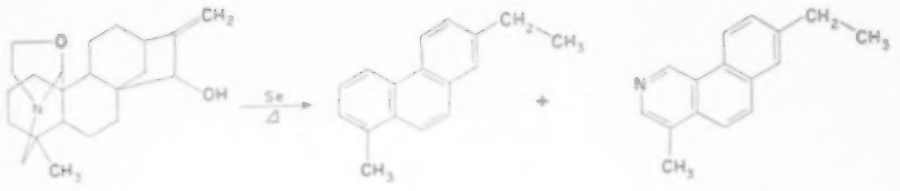
methyl group in pimanthrene (5).[14] Another key development leading to a clarification of veatchine chemistry was the elucidation, by X-ray crystallography and synthesis,

[7] J. Broughton, *Blue Book* 133 (1877).
[8] M. D. v. Wasowicz, *Arch. Pharm.* **214**, 193 (1879).
[9] A. Wright, *Yearbook Pharm.* 422 (1879).
[10] H. A. D. Jowett, *J. Chem. Soc.* **69**, 1518 (1896).
[11] A. Lawson and J. E. C. Topps, *J. Chem. Soc.* 1640 (1937).
[12] For leading references see W. A. Jacobs, *J. Org. Chem.* **16**, 1593 (1951).
[13] K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Canad. J. Chem.* **30**, 608 (1952); K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong and J. A. Edwards, *Chem. Ber.* **86**, 800 (1953).
[14] K. Wiesner, J. R. Armstrong, M. F. Bartlett and J. A. Edwards, *J. Amer. Chem. Soc.* **76**, 6068 (1954).

of the structure of the $C_{16}H_{15}N$ azaphenanthrene (8) obtained by dehydrogenation of veatchine (6).[15a,16] With the veatchine structure clarified, the striking parallelism



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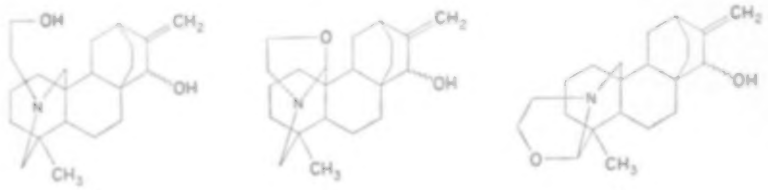
between the chemistry of atisine as uncovered by Jacobs[12], and that of veatchine led Wiesner to suggest a structure for dihydroatisine (9)[15a] and by implication for atisine (10) and isoatisine (11).[15b] Though the Wiesner postulate was based mainly on



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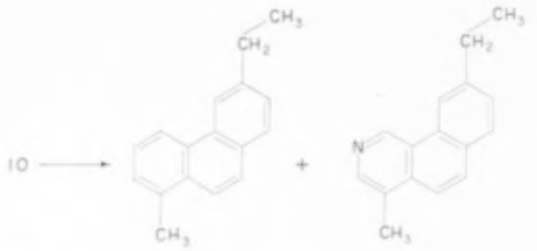
analogy, and direct evidence for many elements of this proposal was lacking, subsequent studies at the Rockefeller Institute and the National Research Council in Ottawa have provided the desired experimental proof for these structures. Thus rigorous proof for the existence of the oxazolidine moiety in atisine[17] and the β-hydroxyethyl group[18] in dihydroatisine, as well as valuable degradative data locating the site of functional groups and shedding general light on the structure,[19–23] was soon forthcoming. Recent advances include proof of the position of the nitrogen atom in atisine,[24] evidence for the presence of a 2,2,2-bicyclooctane system,[25] correlation of ajaconine,[26,27] atidine[27] and the Garrya alkaloids (veatchine and garryfoline) with atisine,[28] a method of removing the nitrogen atom from the diterpene alkaloids,[29] and elucidation of the stereochemistry of the atisine-type alkaloids.[30] These developments will now be surveyed.

[15a] K. Wiesner, J. R. Armstrong. M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954). [b] *cf. Experientia*, **11**, 255 (1955).
[16] M. F. Bartlett and K. Wiesner, *Chem & Ind.* 542 (1954).
[17] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **76**, 4496 (1954).
[18] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4144 (1956).
[19] O. E. Edwards and T. Singh, *Canad. J. Chem.* **32**, 465 (1954).
[20] S. W. Pelletier and W. A. Jacobs, *Chem. & Ind.* 1385 (1955).
[21] O. E. Edwards and T. Singh, *Canad. J. Chem.* **33**, 448 (1955).
[22] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4139 (1956).
[23] D. Dvornik and O. E. Edwards, *Canad. J. Chem.* **35**, 860 (1957).
[24] D. M. Locke and S. W. Pelletier, *J. Amer. Chem. Soc.* **80**, 2588 (1958); *Ibid.* **81**, 2246 (1959).
[25] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 623 (1958).
[26] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 952 (1957).
[27] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).
[28] S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).
[29] O. E. Edwards and R. Howe, *Proc. Chem. Soc.* 62 (1959).
[30] A. J. Solo and S. W. Pelletier, *Chem. & Ind.* 1108 (1960).

B. *Gross structural features*

An important piece of evidence bearing on the skeleton of atisine (10) is the structure of the $C_{16}H_{15}N$ base obtained initially by Lawson and Topps[11] and later by Jacobs[31] from the dehydrogenation of atisine. This base, together with the 1-methyl-6-ethylphenanthrene (12)[31,32] also obtained, accounts for all but three carbon atoms of atisine and relates the heterocyclic ring to the rest of the molecule. By analogy with veatchine chemistry,[33] it would be expected to have the structure of 1-methyl-6-ethyl-3-azaphenanthrene (13). This has been demonstrated by an unambiguous synthesis from 7-ethyltetralone-1.[24] This synthesis provides the first positive evidence fixing the position of the nitrogen atom with respect to the remainder of the atisine molecule.



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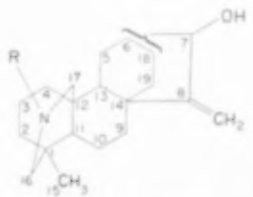
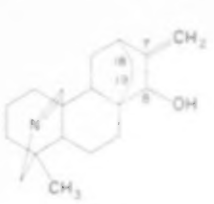
The relative positions of the secondary alcohol and exocyclic methylene groups in atisine were assigned on the basis of the selenium dehydrogenation products.[15a,17] Thus atisine, oxoisoatisine and tetrahydroatisine give 1-methyl-6-ethylphenanthrene (12) while the di- and tricarboxylic acids from isoatisine give 1,6-dimethylphenanthrene.[12,31,32] By analogy with veatchine (6) which gives 1, 7-disubstituted phenanthrenes,[13] the secondary hydroxyl and exocyclic methylene functions were located as in (10).[15a,17] Though cleavage between the carbons bearing the hydroxyl and methylene groups might be expected during dehydrogenation and would account for the formation of the 6-ethyl group, it is not inconceivable that the allylic alcohol and exocyclic methylene groups are reversed in position as in (14). Aside from the suggestive nature of the dehydrogenation data, all the above chemical evidence in both the atisine and veatchine series could have been accommodated as well by structures (14) and (15) respectively.



14 C(7)–C(6) bond
15 C(7)–C(18) bond

[31] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **143**, 589 (1942).
[32] C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.* **170**, 203 (1947).
[33] When dehydrogenated veatchine gave 1-methyl-7-ethylphenanthrene (7)[12] and 1-methyl-7-ethyl-3-azaphenanthrene (8)[16] while atisine gave 1-methyl-6-ethylphenanthrene (12)[31,32] and the unknown $C_{16}H_{15}N$ base.

Definitive evidence on this point is now available in the case of atisine. Dvornik and Edwards have shown that hydration of the C_{20}-azomethine alcohol (16)[24] gave the diol (17) which on reduction, acetylation, selective hydrolysis and oxidation gave a 7,8-*seco*-methylketo acid (18).[25] Treatment of the latter with trifluoroacetyl peroxide followed by hydrolysis and dichromate oxidation gave the bisnor-keto acid (19), 1712 cm^{-1}, 1602 cm^{-1}. Dibromination of (19) followed by dehydrohalogenation gave a crystalline phenol (20) [828, 1586, 1638 cm^{-1}, λ_{max} 282 mμ shifting to 300 mμ in alkali], and a keto γ-lactone (1796, 1734, 1639 cm^{-1}). Formation of the latter,



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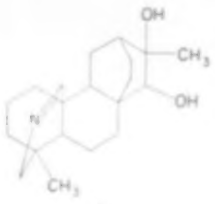

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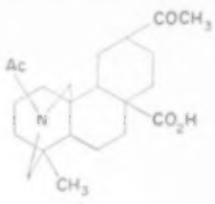

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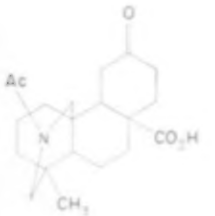

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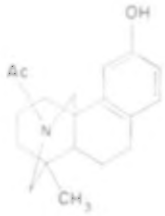

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involving displacement of bromine α to the keto group by carboxylate anion, demonstrates a 1,4 relationship of the ketone and carboxyl groups in (19). Thus these results, when taken with Jacobs dehydrogenation evidence for substitution at C-6,[12,32] show clearly that a 2,2,2-bicycloöctane system is present in atisine and that the terminal methylene group is located at C-7 (or C-18)[37] and the secondary hydroxyl at C-8 (or C-19)[37] respectively.[25] Further evidence on this point is provided by the following sequence of reactions.[38] Isomerization of isoatisine (11) with ethanolic hydrochloric acid gave a mixture of ketones (21) [1712 cm^{-1}] epimeric at the adjacent methyl group. That skeletal rearrangement had not occurred during the isomerization was shown by borohydride reduction of (21) to give a mixture from which the known α-tetrahydroatisine (22)[39] was isolated. Removal of the keto group to give (23) could be effected only by Barton's procedure[40] for sterically hindered ketones. That the oxazolidine ring was opened is not surprising since it is well known that both atisine

[24] This unusual and valuable degradation product was first obtained as a by-product of the permanganate oxidation of atisine.[15,22,23] Subsequently a useful procedure of preparation involving a Hofmann degradation of atisine diacetate chloride was published.[22,26]

[25] S. W. Pelletier, Lecture, Gordon Research Conference on Steroids and Related Natural Products, New Hampton, N.H., August 24, 1955.

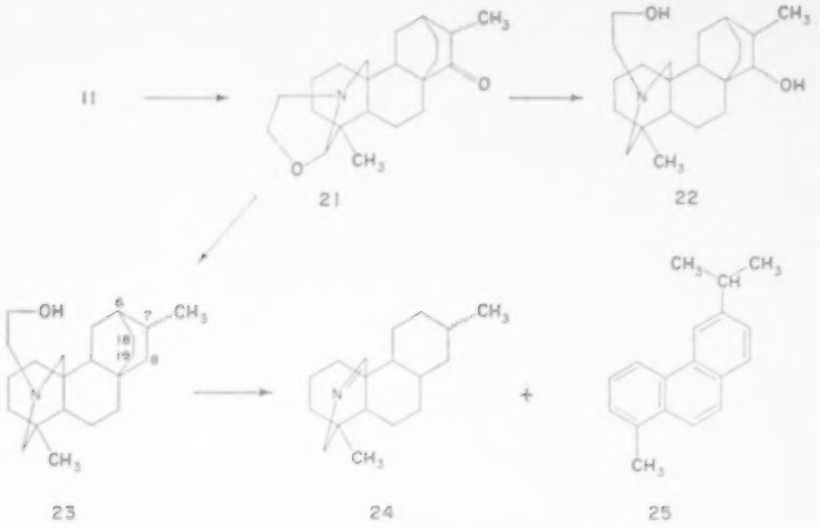
[26] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 248 (1956).

[37] Since the bicycloöctane system is symmetrical, the allylic alcohol system could be located on either the *cis*- or *trans*-branch. This point will be considered later under the section on the stereochemistry of atisine.

[38] S. W. Pelletier, *Chem & Ind.* 1116 (1958).

[39] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **143**, 589 (1942).

[40] D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.* 2056 (1955).



and isoatisine are reduced to dihydroatisine (9) when heated with ethanolic alkali at high temperatures.[41] Dehydrogenation of (23) with selenium gave the epimeric azomethines (24) and also 1-methyl-6-isopropyl phenanthrene (25).[38] Had the methylene group been located at C(8) or C(19)[37] one would expect to obtain either 1,6-dimethylphenanthrene or 1-methyl-6-n-propylphenanthrene. The formation of the isopropyl derivative is again clear evidence for assigning the methylene group to C(7) or C(18).[37,38] Aside from stereochemical features, which are discussed in another section, atisine is thus shown to have structure (10).

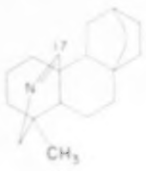
C. *Removal of the nitrogen from diterpene alkaloids*

Of significance relative to the problem of degrading the atisine alkaloids to diterpenes of established stereochemistry is the difficulty in removing the nitrogen atom. Since both positions β to the nitrogen are quaternary, Hofmann type degradations are ineffective. What might appear to be a particularly susceptible group for an attack on the nitrogen is the azomethine linkage such as occurs in (26). This masked aldehyde manifests a remarkable stability to both acids and bases. Thus it survives boiling with 10 per cent hydrochloric acid[42] and also conditions of the Wolff-Kishner reaction.[23,43] The remarkable stability of this function is owing to the peculiar geometry of the system. Steric compression between the nitrogen and C(17) maintains the linkage in a closed position, thus effectively prohibiting reactions which would normally occur via the aldehyde.

Recently success in removing the nitrogen from (26) has been achieved through a mild reaction with aqueous nitrous acid.[29,44] Treatment with nitrous acid gave as the major product a hemiacetal (27) which was oxidized with bromine water to a δ-lactone (1725 cm^{-1}). The hemiacetal was converted successively to a primary alcohol (28a),

[41] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **147**, 567 (1943).
[42] S. W. Pelletier, unpublished work.
[43] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 952 (1957).
[44] Reactions of a similar type have been studied in the case of amides and amines by R. Huisgen and his collaborators [*Leibigs Ann.* **599**, 161, 183 (1956); *Ibid.* **601**, 1 (1956)].

aldehyde (1696 cm^{-1}) (28b) and carboxylic acid (1675 cm^{-1}, λ_{max} 225 mμ, ε100) (28c). It is of interest to note that the sodium salt of (28c) is soluble in ether and that it has a



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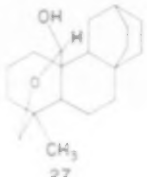

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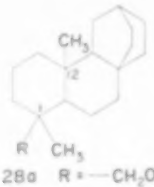


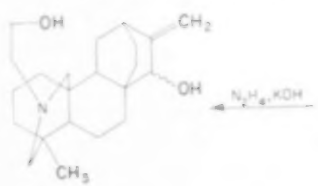
28a R = —CH_2OH
28b R = —CHO
28c R = —CO_2H

pKa of 9·6. The abnormal ultraviolet absorption of the acid and the displaced infrared maxima of the lactone, aldehyde and acid are attributed to the extreme steric hindrance of the carbonyl groups. That (28c) is an extremely weak acid is probably due to steric hindrance of solvation of the carboxylate ion.[29]

Note added in proof: Djerassi (private communication, Dec. 22, 1960) has shown in the case of the azomethine from garryfoline that the angular carboxyl is located at C(12) rather than at (C1). [Diterpene numbering, see formula 63a] Structure (27, 28a, b, c) should also be revised accordingly.

III. THE STRUCTURE OF ATIDINE

Atidine, $C_{22}H_{33}NO_3$, has been isolated from the strongly basic fraction of extracts of *Aconitum heterophyllum*.[45] Chemical and infrared data indicate that two of the oxygen atoms exist as primary or secondary hydroxyls (diacetate) and the third as a ketone (oxime) in a six- or larger-membered ring (1695 cm^{-1}). Also present are an exocyclic methylene group (3086, 1658, 900 cm^{-1}; formaldehyde results from permanganate-periodate oxidation), a C-methyl group (1376 cm^{-1}) and a N—CH_2CH_2OH group.[45] The conclusion that atidine is a keto dihydroatisine was shown to be correct by conversion of atidine (29) to dihydroatisine (30) by the Huang-Minlon procedure.[46] Possible sites for the keto group were indicated by observation that treatment of atidine with alkali under mild conditions led to extensive formation of polymeric material.[42] With a keto group at either position 9 or 19 one would expect the β-hydroxyketone to undergo facile cleavage of the retroaldol type to give the unstable acrolein derivative (31), thus accounting for the rapid destruction of atidine. Sub-



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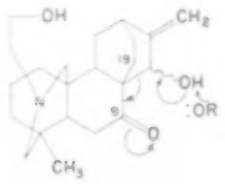

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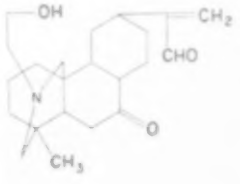


31

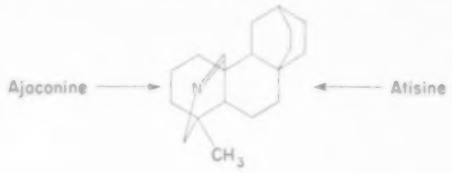
sequent correlation of atidine and ajaconine via the dihydro derivative (*vide infra*)[46]

[45] S. W. Pelletier, *Chem. & Ind.* 1016 (1956).
[46] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).

and the elucidation of the structure of ajaconine[47] allow the keto function to be assigned to position 9 in atidine (29).

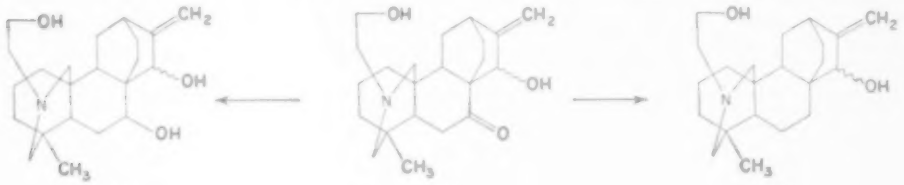
IV. THE CHEMISTRY OF AJACONINE

The delphinium alkaloid ajaconine[48] (*D. ajacas*), $C_{22}H_{33}NO_3$, is of especial interest since it is the first reported example of an atisine derivative occurring in a delphinium species.[43] Ajaconine was shown to have the same carbocyclic skeleton as atisine by conversion to the oxygen-free azomethine base (32), earlier obtained from atisine.[23,43]



32

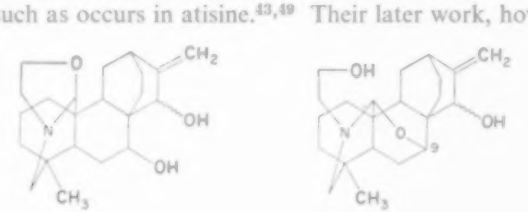
That the secondary allylic alcohol system also has the same position and stereochemistry in ajaconine as in atisine was shown by the reduction of atidine (29), a companion of atisine,[45] to a mixture of epimers, one of which is identical to dihydroajaconine



33 29 34

(33).[46] Since atidine had been previously converted to dihydroatisine (34), it is clear that ajaconine is a derivative of the latter.[46]

Initial observations on the behavior of ajaconine, including its high pK_a' (11·3), formation of an anhydronium chloride (I.R., 1683 cm^{-1}, $\rangle C{=}\overset{+}{N}\langle$) and the smooth Hofmann-type elimination of the acetoxyethyl group of ajaconine triacetate to give an azomethine base, led Dvornik and Edwards to assume it contained an oxazolidine ring system (35) such as occurs in atisine.[43,49] Their later work, however, has shown

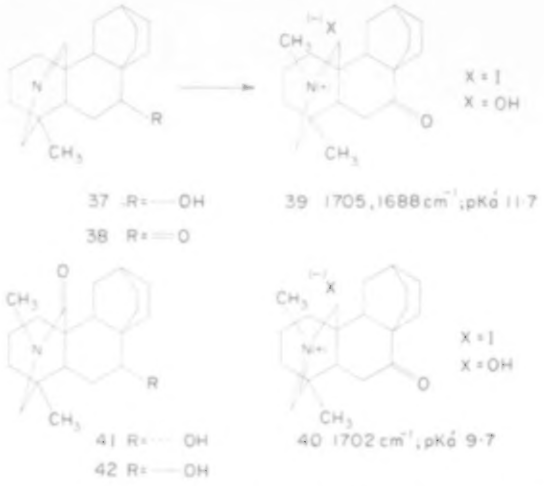


35 36

that the internal carbinolamine ether involves the 9-oxygen atom and is not derived from the N-2β-hydroxyethyl system as in atisine. The subsequent discussion of ajaconine chemistry will be based therefore on this revised structure (36).[47]

[47] D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.* 305 (1958).
[48] J. A. Goodson, *J. Chem. Soc.* 245 (1945).
[49] D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.* 280 (1958).

The position and character of the hydroxyl group resulting on opening of the ether ring was established as follows.[49] The C_{19}-alcohol (37) was oxidized to the corresponding ketone (38) and thence converted to the N-methyl carbinolamine (39). Hot methanolic alkali transformed (39) into a mixture of the corresponding iso compound (40) and a hydroxy lactam (41)3380, 1054, 1620 cm^{-1}. The latter was

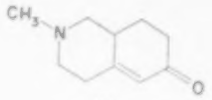


shown to result from an intramolecular Cannizzaro-type reaction. Oxidation of (41) followed by reduction gave the epimeric hydroxy lactam (42) with the hydroxyl in the original orientation of ajaconine. Spectroscopic data indicate that the hydroxyl in (41) is axial (1054 cm^{-1}) and in (42) is equatorial (1082 cm^{-1}). The above evidence demonstrates the hydroxyl in (41) is *trans* to the N-bridge and in (37) is *cis* thereto. The hydroxyl was shown to be at position 9 by the following sequence.[49] Azomethine (37)

was converted rationally to ketone (43). Bromination of the latter gave a monobromo ketone which on dehydrobromination gave the α,β-unsaturated ketone (44), 1664 cm^{-1}, λ_{max} 250 mμ (ε9300) and 328 mμ (ε96) in ethanol. The ultraviolet maximum at 250 mμ corresponds reasonably well with the calculated value of 244 mμ[50,51] for a β,β-disubstituted exocyclic double bond, though certain basic α,β-unsaturated ketones have been shown to absorb at abnormally short wave lengths, e.g. compound (45) is reported to absorb at 227·5 mμ in methanol,[52] and at 232 mμ in ethanol.[53]

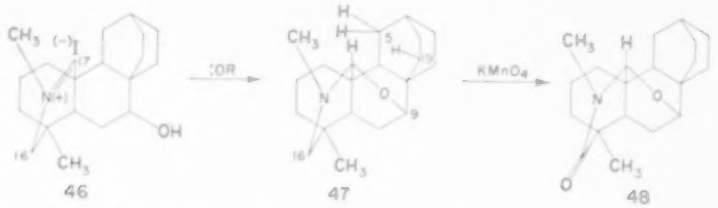
[50] R. B. Woodward, *J. Amer. Chem. Soc.* **63**, 1123 (1941); *Ibid.* **64**, 76 (1942).
[51] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene* p. 190. Reinhold, New York (1949).
[52] C. B. Clarke and A. R. Pinder, *J. Chem. Soc.* 1967 (1958).
[53] E. M. Kosower and D. C. Remy, *Tetrahedron* **5**, 281 (1959).

However, (45) may not be a good model since the geometry of the heterocyclic ring is different in (44).



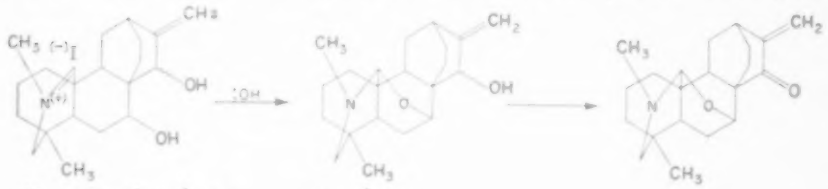
45

That the carbinolamine function in ajaconine is derived from the 9-oxygen is suggested by the behavior of the methiodide (46) with hot, methanolic alkali.[47] The product is a hydroxyl-free base (47) [pK_a' 10] and hence must be an internal cyclization product derived from the 9-hydroxyl and carbon 17 or 16. Since oxidation of (47) with permanganate gives a carbinolamine ether lactam (48) [1655 cm^{-1}] with the amide



46 47 48

carbonyl at C(16),[54] it is clear that C(17) is involved in ether formation in (47). A second parallel series of transformations involving the methiodide (49) is more convincing since the products are more closely related to ajaconine.[47] Conversion of (49) to (50) with cold base and subsequent oxidation with manganese dioxide gave the



49. 1685 cm^{-1}; pKá 10·5 50 pKá 10·6 51

hydroxyl-free α,β-unsaturated ketone (51), pK_a' 9·0, 1706 cm^{-1}, λ_{max} 222 mμ (ε6840). Since base 50 and ajaconine have identical pK_a' values (10·6) and equal rotations, it is reasonable to believe they are analogous compounds.

The fact that the carbinol amine ethers (47) and (50) are not isomerized by alkali to C(16)—O—C(9) ethers led Edwards to postulate that the driving force for the atisine-isoatisine type isomerization is the relief of steric compression between the C(17) oxygen and the 5(H) atom.[47] While this explanation has some validity it will be shown later to be incapable, by itself, of accounting for the sizable free energy difference between atisine and isoatisine (see p. 91).

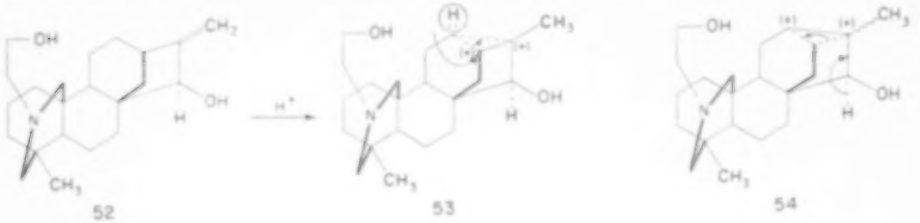
V. THE CORRELATION OF THE ATISINE AND GARRYA ALKALOIDS

In a recent review Wiesner recounts an attempted correlation of the Garrya alkaloids and atisine by vigorous acid isomerization of dihydroveatchine.[55] It was

[54] Formation of a 17-carbonyl group by intermolecular oxidation is not possible because of the inaccessibility of the 17-hydrogen atom [facing C(19)].[47]

[55] Reference 4, page 52.

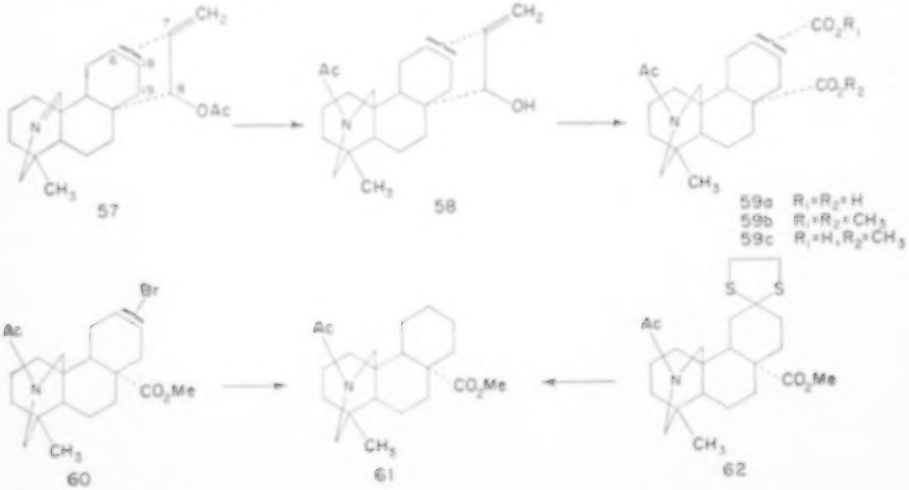
anticipated that the bridged cation (53) formed by protonization of dihydroveatchine (52) might be slowly transformed by a hydride shift to bridged cation (54) which could then ketonize as indicated to give "tetrahydro-ketoisoveatchine" (55). If atisine has the stereochemistry in the C/D rings predicted by Wenkert's biogenetic



52 53 54

56 55

scheme,[56] compound (55) should be identical with "tetrahydro-ketoatisine". Isomerization of dihydroveatchine under vigorous acidic conditions did indeed give a ketone (carbonyl frequency characteristic of a cyclohexanone) which was tentatively concluded to have structure (55). However, comparison with an authentic sample of "tetrahydro-ketoatisine", showed the compounds were *not* identical. Wiesner points out the uncertainty of the structure assigned to "tetrahydroketoisoveatchine", but suggests that the simplest interpretation of this work would be the assignment of structure (55) to "tetrahydro-ketoisoveatchine" and structure (56) to "tetrahydro-ketoatisine".[56] This would mean that if atisine has the usual *trans-anti* backbone



57 58 59a $R_1=R_2=H$ 59b $R_1=R_2=CH_3$ 59c $R_1=H, R_2=CH_3$

60 61 62

[56] E. Wenkert, *Chem & Ind.* 282 (1955).

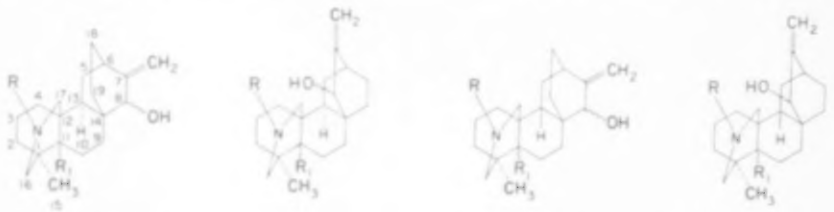
common to most diterpenes, the allylic alcohol would occupy the *cis* bridge (with respect to nitrogen) of the bicyclo-(2,2,2)-octane system. However, our own results[38] and those of Edwards[25] clearly indicated otherwise, so it was of interest to effect a correlation of atisine and the Garrya alkaloids by a less ambiguous procedure. This was accomplished by converting both atisine and veatchine, by a parallel sequence of degradations, to the same N-acetyl ester (61).[28] The respective azomethine acetates (57) derived from atisine [C(7)—C(6) bond] and veatchine [C(7)—C(18) bond] were converted to the N-acetyl derivatives (58) by reduction, acetylation and saponification. Oxidation of (58) with permanganate-periodate under carefully controlled conditions gave the respective dicarboxylic acids (59a). Saponification of the dimethyl esters (59b) gave (59c) which were transformed to the monobromides (60) utilizing the Hunsdiecker reaction. Reductive debromination of (60) with zinc in acetic acid gave (61). Compound (61) was also obtained from atisine by another route. Desulfurization of the thioketal (62) derived from (19)[25,58] gave a product identical with (61.)[57]

The formation of (61) from both atisine and veatchine demonstrates that these compounds as well as the related alkaloids, garryfoline,[59] atidine[46] and ajaconine,[47] all have the same stereochemistry.

VI. STEREOCHEMISTRY OF THE ATISINE AND GARRYA ALKALOIDS

A. *The carbon skeleton*

It has been common to assume that alkaloids of the atisine and veatchine types have the *trans-anti* skeleton which is common to most diterpenes, though until recently no evidence supporting this assumption was available.[23,25,38,59] *A priori*, eight *dl*-pairs, of which four are A/B-*trans*-isomers (63 a–d) and four are A/B-*cis*-

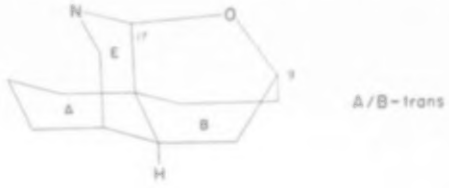


(63a) R_1 = α-H (63b) R_1 = α-H (63c) R_1 = α-H (63d) R_1 = α-H
(64a) R_1 = β-H (64b) R_1 = β-H (64c) R_1 = β-H (64d) R_1 = β-H

isomers (64 a–d), are possible on the basis of the chemistry discussed thus far for atisine. The work of Dvornik and Edwards[47] on ajaconine (see p. 83) is significant relative to the stereochemistry of atisine. Their results have been utilized recently by Solo and Pelletier to define certain aspects of the stereochemistry of atisine and the Garrya alkaloids.[30] Thus briefly, the existence of an ether bridge between C(9) and C(17) of ajaconine (36)[47] and its derivatives requires that the ether oxygen and C-17 be in a 1,4-*cis-diaxial* relationship to each other on ring B. Since it can be shown that only the *cis*-perhydroisoquinoline system with an A/B-*trans*-fusion (65) satisfies this

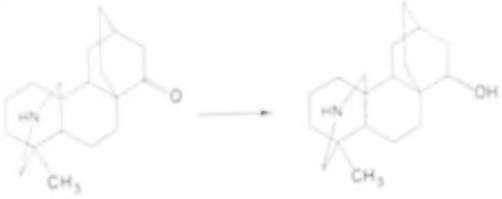
[57] S. W. Pelletier and D. M. Locke, unpublished work.
[58] We thank Dr. O. E. Edwards for placing at our disposal the experimental directions for the preparation of the intermediate diol (17).
[59] C. Djerassi, C. R. Smith, S. K. Figdor, J. Herran and J. Romo, *J. Amer. Chem. Soc.* **76**, 5889 (1954); *Ibid.* C. Djerassi, C. R. Smith, A. E. Lipmann, S. K. Fidgor and J. Herran, **77**, 4801, 6633 (1955).

requirement, A/B-*trans*-isomers (63 a–d) remain for consideration.[30] Differentiation between isomers (63a and b), in which a *trans-anti* backbone is present, involves the choice of locating the allylic alcohol group on the *trans*-(isomer a) or *cis*-branch (isomer b) of the bicyclo [2,2,2] octane system. Reduction of ketones (66)[25] and (68)[26]

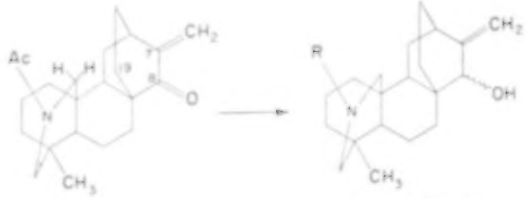


65

with sodium borohydride gives in each case a pair of epimeric alcohols (67a, b and 69a, b), each of which readily forms an O-acetate. This relatively unhindered character of the hydroxyl groups supports location of the allylic alcohol group on the *trans*-bridge (isomer 63a) of the bicycloöctane system, for if the group were on the *cis*-branch (isomer 63b) only one epimer would be expected on reduction due to the severe crowding at C(19). Moreover, this view is confirmed by a study of the epimeric N-ethyl compounds (70a and b) and their pK_a's.[38,42]

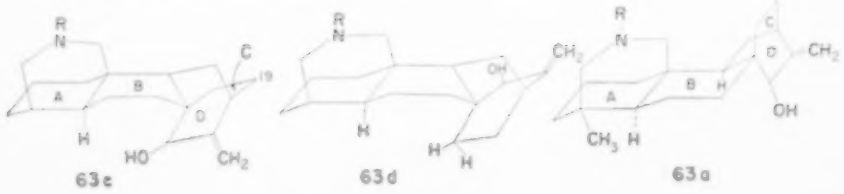


66 67a,b



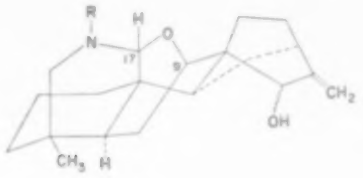
68 69a,b, R = Ac
70a,b, R = Et

The choice between isomer (63c) and (63d) of the *trans-syn*-perhydrophenanthrene system may be made by noting that the condition of relatively unhindered hydroxyls in (67), (69) and (70) is met only in (63d), but not in (63c). Thus the above arguments rigorously limit the stereochemistry of atisine to either (63a) or (63d).[30]



63c 63d 63a

Differentiation between 63a and 63d is possible on the basis of two observations from ajaconine chemistry:[30] i, a very large negative shift in rotation accompanies formation of the C(9)—C(17) oxide bridge and ii, spectral data show that the hydroxyl derived by opening the C(9) oxygen of ajaconine is *equatorial*.[47] If isomer (71) represents ajaconine, the open form (72) may be pictured as having ring B as a chair with an equatorial hydroxyl at C(9) which is transformed to a boat in the closed form. Since a major conformational change is involved in this transformation, one would expect a dramatic shift in rotation—which is in fact noted.



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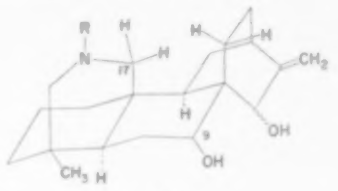

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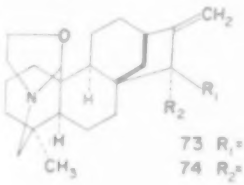
If, however, ajaconine has the stereochemistry of isomer (63d), the hydroxyl at C(9) must be pseudo-axial to be able to bridge to C(17). But the C(9) hydroxyl is known to be equatorial.[47,49] Furthermore, formation of an ether bridge between C(9) and C(17) would merely distort, but not invert ring B, thus not accounting for the observed rotation shift. Finally, the required bond distortion would create severe strain in the bicycloöctane system. For these reasons, it is clear that ajaconine and therefore atisine and atidine can have only the ABD *trans-anti-trans* skeleton of (63a).[30] Since veatchine and garryfoline have been correlated with atisine[28] they have the same stereochemistry and may be represented by structures (73) and (74) respectively.



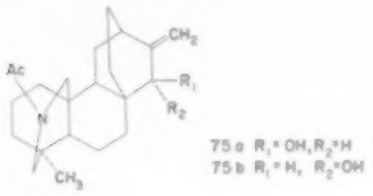
73 R_1 = —OH, R_2 = H
74 R_2 = —OH, R_1 = H

B. *The configuration of the allylic hydroxyl in atisine*

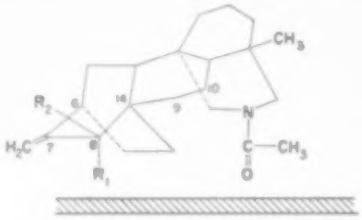
The tentative assignment of the allylic hydroxyl in atisine was originally made on the basis of the marked difference in absorption behavior toward alumina of the epimeric alcohols (75a) and (75b). Since models suggest that a hydroxyl with the configuration as in (75a) (OH *cis*- to nitrogen) is slightly more shielded than (75b), the less firmly bound epimer (with the natural configuration) was assumed to be (75a).[39] However, the difference in steric environment seems too small to account for the great difference in absorption behavior of these compounds. Further consideration[60] reveals that in isomer (75a), the hydroxyl and N-acetyl group are so oriented that they may be absorbed simultaneously on the alumina surface. This may most clearly be seen by viewing the molecule along the plane described by atoms C(6), C(7), C(8), C(14), C(9) and C(10) as shown below. In isomer (75b) the hydroxy land N-acetyl

[60] S. W. Pelletier and D. M. Locke, unpublished observation.

group are on opposite sides of the molecule and therefore cannot be absorbed by the alumina at any given time. The more strongly absorbed isomer must be (75a) in which hydroxyl and N-acetyl absorption reinforce each other. Atisine, which has the



75a R_1 = OH, R_2 = H
75b R_1 = H, R_2 = OH



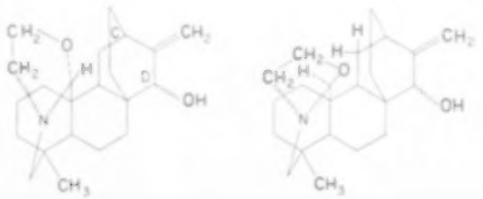
configuration of the less strongly absorbed of the two isomers, must be represented by the configuration of (75b). Since atidine and ajaconine have been correlated with dihydroatisine,[27] the allylic alcohol group in these compounds would also have the α-configuration as in (75b). It is interesting to note that the allylic hydroxyl in garryfoline also has the α-configuration.[59]

C. *The conformation of the E/F rings in atisine*

There remains the question of the steric arrangement of the E and F rings of atisine (76) and its bearing on the atisine-isoatisine type of isomerization.[61] The

76 77

piperidine ring E of atisine could in principle exist in either a boat or chair conformation and, to each of these, ring F could be fused so as to give two *cis*-forms and one *trans*-form, giving a total of six conformers. Three of these may be eliminated by the following argument. Very great hindrance is known to exist between the 17-methylene group and the C(18)—C(19) bridge of atisine (76).[15b,20] Since the oxazolidine ring may be reformed easily from derivatives in which C(17) is trigonal (77),[20] the 24

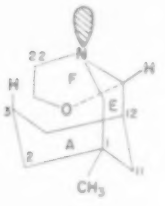


78 79

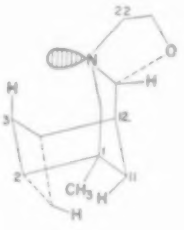
oxygen atom in atisine must be substituted on the less hindered side of C-17—i.e. the side away from ring C (formula 78). The three conformers corresponding to 79 are thereby eliminated.[61]

[61] A. J. Solo and S. W. Pelletier, *Proc. Chem. Soc.* 14 (1961).

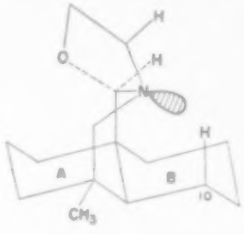
The conformers, (X,Y,Z), corresponding to (78) may now be considered. Conformer (X) in which ring-A is a chair with C(22) axial is unlikely since the A and F rings are strongly opposed. The free electron pair on nitrogen is hindered by a hydrogen on C(3) in conformer (Y) and by a hydrogen on C(10) in conformer (Z). The interaction at C(3) in (Y) is relieved with ring A as a boat but such a change introduces new interactions. It should be noted that with either form the ring system of atisine must be distorted so as to accommodate the very serious interactions between rings C and E. This distortion has the effect of relieving the $N—H_{C(10)}$ interaction in (Z) but of increasing the interaction of the hydrogen atoms in the flagpole positions of boat A in (Y). Moreover, the the five-membered F-ring is *trans*-fused to E in (Y) and this tends to distort E in such a way as to increase the hindrance encountered by the nitrogen. In rotamer (Z), however, the *cis*-fused E/F junction tends to relieve the interaction suffered by nitrogen with the hydrogen on C(10). Finally, as will be shown below, the oxygen of oxazolidine ring-F is seriously hindered in (Y) but is not in (Z). Therefore, these factors indicate that conformation (Z) should be at least as stable as (Y).[61]



78x



78y



78z

It has been noted that conversion of C(17) in atisine derivatives from a quaternary to a trigonal form results in a considerable decrease in strain.[4] This reduction in steric hindrance provides the accepted explanation for the high pK_a of atisine (12·8)[20] and also provides a reasonable explanation for the fact that the diacetate of isoatisinium chloride is readily isomerized to the corresponding atisine derivative.[21] Since both atisine and isoatisine have quaternary C(17) groups, it is necessary to look further for the reason for the facile isomerization of atisine to isoatisine, or in other words for the greater stability of isoatisine over atisine (a free energy difference of at least 3 kilocalories is required).[62,63] Dvornik and Edwards have explained the stability difference on the basis of an interaction between the C(24) oxygen of ring-F and the C(5)-hydrogen which occurs in atisine, but not in isoatisine.[47] This interaction may be observed in models of rotamer (Y), but not in (Z). To the extent that steric strain results from this interaction, rotamer (Z) should be favored over (Y). Therefore

[62] A. J. Solo and S. W. Pelletier, unpublished work.

[63] The statement that ΔF for the atisine-isoatisine conversion equals 3 kcal minimum assumes that at 25°C the equilibrium atisine $\rightleftharpoons$ open form lies at least 93 per cent toward the open form and that in refluxing ethanol the open form is converted at least to the extent of 91 per cent to isoatisine.

Thus $\Delta F = RT \ln K = 4{\cdot}58 \times 298 \log 93/7 = 1{\cdot}52$ kcal.

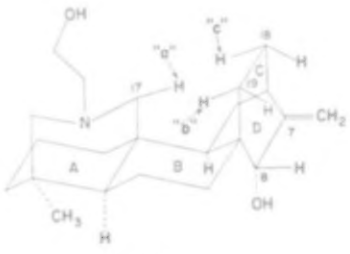
and $\Delta F = RT \ln K = 4{\cdot}58 \times 338 \log 91/9 = \underline{1{\cdot}56 \text{ kcal.}}$

$3{\cdot}08$ kcal.

If the equilibria lie less far to the right than assumed, ΔF_{min} must be reduced, but it will certainly be far more than the 0·4 kcal which Edwards' O(24)—C(5)H interaction makes available through entropy factors, (see footnote 64).

unless (Z) can be shown to be less stable than (Y), this interaction by itself cannot explain the free energy difference between atisine and isoatisine.[64]

If dihydroatisine (80) is constructed using Dreiding[65] or other models in which atoms have no bulk, but in which the bonds are rigid, tetrahedral angles are preserved, free rotation about single bonds is possible and covalent bond distances are correct; then, hydrogen "a" on C(17) may be seen to be strongly hindered by hydrogens on the C(18)—C(19) bridge. Depending on the staggering of the bicycloöctane system, the distance between hydrogen "a" and hydrogen "b" on C(19) varies from 1·26 to 1·38 Å, while the distance between "a" and "c" varies from 1·27 to 1·66 Å—all without introducing angular strain.[62] These distances are all well under the required internuclear separation of approximately 2·4 Å (2 × the van der Waals radius of hydrogen = 2 × 1·2 Å). Since the energy required to deform bond angles of a molecule is always less than the energy gained by moving interfering groups apart,[66] the steric compression of hydrogen "a" will be accommodated by distortion of the dihydroatisine ring system. To relieve the steric hindrance, it is necessary that the bonds from the perhydrophenanthrene system ABD to C(18) and C(19) should bend away from the bond to C(17) and vice-versa. (Formula 80). While the greater part of the indicated accommodation undoubtedly affects mainly the B—C—D system, movement



80

of C-17 is also important. The motion which C-17 may undergo involves bending away from ring C and rotating in such a way as to make the axial bond on C-17 even more axial and the equatorial bond—more equatorial.

This rotation of the C-17 group is in the direction opposite to that which would be required to form the (angular strain-free) conformer (78Z) of atisine. In isoatisine C-17, not being part of the oxazolidine system, is free to undergo essentially the same rotation as it undergoes in dihydroatisine. The greater free energy of atisine as compared to isoatisine may therefore be attributed to the increased steric hindrance in atisine caused by the restriction which ring F imposes on the rotation of C-17. The steric compression is of course still accommodated by the distortion of the molecule as a whole, but the net effect is an increase in bond distortion with a concomitant increase in energy.[61]

Leonard has recently studied the isomerization of a tricyclic oxazolidine model of

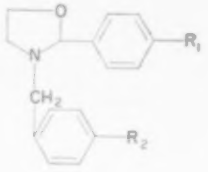
[64] Position C(16) is relatively unhindered, therefore in isoatisine the oxygen of ring F may be attached to either side of ring E. This extra degree of freedom should permit an extra conformer (ring-E as a chair with C(22) equatorial but with *cis*-E/F-fusion) to exist in isoatisine. The resulting increase in entropy for isoatisine could contribute a maximum of approximately 0·4 kcal. (RT ln 2) toward increasing the stability of isoatisine over atisine.

[65] A. S. Dreiding, *Helv. Chim. Acta* **42**, 1339 (1959).

[66] F. H. Westheimer, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) Chap. 12. John Wiley, New York (1956).

the AEF-ring system of the diterpene alkaloids, viz. 6-aza-3-oxatricyclo [6.3.1.$0^{2,6}$] dodecane (81).[67] Isomerization of this model, in which there is no steric driving

81



82a $R_1 = H, R_2 = OCH_3$

82b $R_1 = OCH_3, R_2 = H$

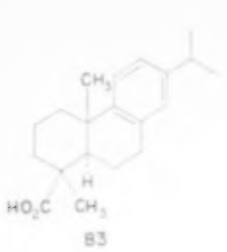
force to rearrangement of the oxazolidine ring, required more strenuous conditions than atisine, veatchine or garryfoline. In another model system of the arylaralkyl-oxazolidine type (82a,b) in which there was no steric differentiation between the two α N-carbons but in which the protons on these carbons were more acidic than in the diterpene alkaloids, isomerization did not occur under conditions which lead to formation of the "iso" alkaloids. These findings indicate that isomerization of ternary iminium compounds is not a general phenomenon but is very dependent upon steric factors and reaction conditions. Incidental to this study a new method of oxidative cyclization for the synthesis of oxazolidines from β-3° aminoalcohols was developed using mercuric acetate. A detailed subsequent study showed that mercuric acetate oxidation of several piperidino- and pyrrolidino-alcohols gave good yields of bicyclic oxazolidines and tetrahydro-1,3-oxazines.[68]

D. *Absolute configuration*

The absolute configuration of the atisine alkaloids has not yet been settled but the scanty evidence available suggests that atisine bears a mirror image relationship to that of the common diterpenes and hence to the above formulas.[25] Thus the phenol (20) derived from atisine shows a strong negative rotation (M_D-314°) whereas the molecular rotations of dehydroabietic acid (83), ferruginol acetate (84) and podocarpic acid (85) are strongly positive. For this reason the atisine phenol has been assigned the configuration shown in formula (86).[25] The fact that lycoctonine and aconitine have been shown to have a configuration antipodal to the common diterpenes[69] is in agreement with this assignment.

Note added in proof: Djerassi and Vorbrüggen (private communication) have recently converted the azomethine from garryfoline to a hydrocarbon via the aldehyde analogous to (28b). This hydrocarbon is not identical with either α- or β-dihydrophyllocladene. Since the rotatory dispersion curves of ring-D ketones of garryine are substantially identical with those of the corresponding ketones of the phyllocladene series, these workers conclude that the absolute configuration of the A/B ring juncture in the alkaloids is antipodal to that of the steroids and common diterpenes.

[67] N. J. Leonard, K. Conrow and R. R. Sauers, *J. Amer. Chem. Soc.* **80**, 5185 (1958).
[68] N. J. Leonard, and W. K. Musker, *J. Amer. Chem. Soc.* **82**, 5148 (1960).
[69] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1843 (1959).



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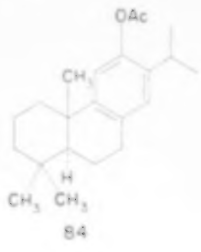

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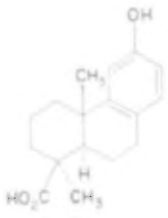

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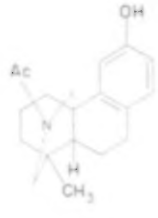

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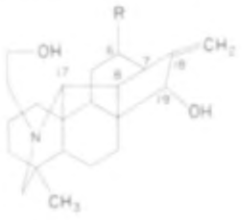
VII. NAPELLINE AND SONGORINE (NAPELLONINE)

As a result of a careful series of investigations, Wiesner was led to assign structure



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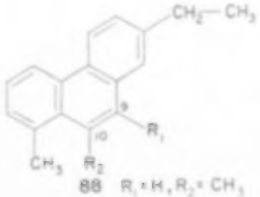
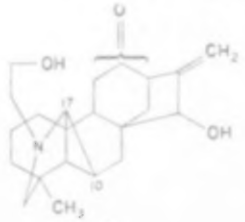
(87) to napelline (R = - - -OH) and napellonine (R = O).[70] Subsequently, Kuzovkov showed the identity of napellonine and songorine and that selenium dehydrogenation of the latter gave a trisubstituted phenanthrene which was identified by synthesis as 1,10-dimethyl-7-ethylphenanthrene (88).[71] He pointed out that this result confirmed the presence of a substituent at the C(1) position and the joining of the five-membered ring at C(7), but made improbable a bond between C(17) and C(8). Instead, bonding from C(17) to C(10) was suggested and structure (90) proposed for songorine[71,72].



88 R_1 = H, R_2 = CH_3
89 R_1 = CH_3, R_2 = H



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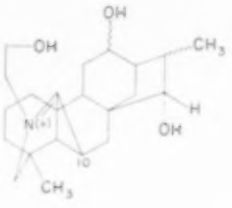
[70] K. Wiesner, Z. Valenta, J. F. King, R. K. Maudgal, L. G. Humber and S. Itô, *Chem. & Ind.* 173 (1957).
[71] A. D. Kuzovkov, *J. Gen. Chem.* **28**, 2320 (1958). English translation.
[72] A. D. Kuzovkov, *J. Gen. Chem.* **29**, 1706 (1959). English translation.

Wiesner pointed out the incompatibility of this structure with formation of a carbinolamine ether from dihydronapelline by oxidation with silver oxide.[4,73] Thus it is clear that a C(17)—C(10) bond in the salt form of the carbinolamine ether (91) is impossible. Subsequently, Wiesner *et al.* showed that formation of glyoxal by oxidation with lead tetraacetate is not a specific reaction for the N—CH_2CH_2OH group and that napelline contains an N-ethyl group.[4,73] The carbinolamine ether was then formulated by Wiesner as (92) and its salt as (93),with a C(17)—C(10) bond. Other



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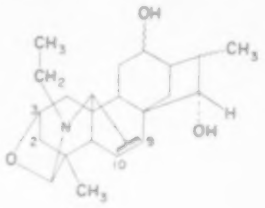

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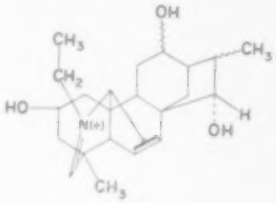

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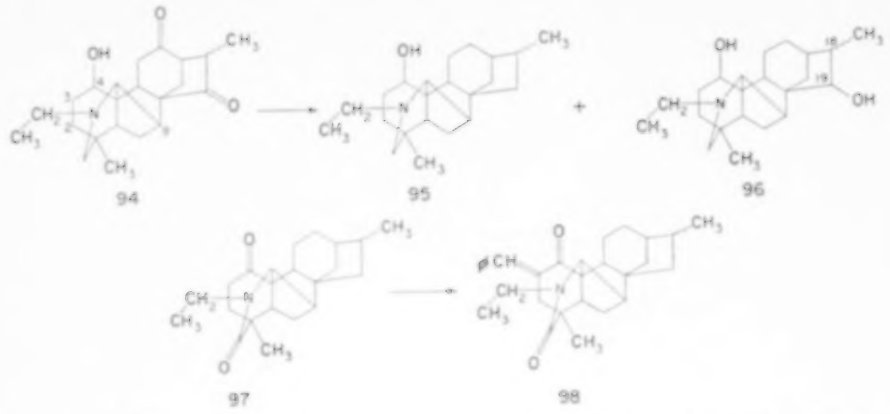
sites for the location of the ether oxygen are of course possible at C(2) or C(4). In considering an alternative and biogenetically more plausible structure for songorine, Wiesner made the attractive hypothesis that rearrangement of the 10-methyl group into the less hindered 9-position had occurred in the last step of Kuzovkov's synthesis of 1,10-dimethyl-7-ethylphenanthrene. The "natural" phenanthrene should then be 1,9-dimethyl-7-ethylphenanthrene (89) and songorine would possess a C(17)—C(9) bond.[4,73] This perceptive suggestion has been shown to be correct by Ochiai *et al.* who have demonstrated that the songorine hydrocarbon is in fact (89) by unambiguous syntheses.[74] It is interesting to note that (89), as well as a small amount of 1,3,9-trimethyl-7-isopropylphenanthrene, is also obtained by the dehydrogenation of isodesoxysongorine (100) hydrochloride.[75,76]

Recently Sugasawa has questioned the assignment of a hydroxyl at C(3) in songorine and in fact has accumulated rather compelling evidence for location of a hydroxyl at C(4).[76,77] This evidence will now be outlined.

Isosongorine (94), [1736, 1695 cm^{-1}], available from the allylic rearrangement of songorine with palladium charcoal, gave on Huang-Minlon reduction dideoxyisosongorine (95) and a small yield of the glycol (96) [3310–3500 cm^{-1}]. Oxidation of (95) with an excess of chromium trioxide-pyridine gave a neutral product which was formulated as a keto δ-lactam (97) [1707, 1635 cm^{-1}]. The latter gave a compound containing 1·82 atoms of deuterium when equilibrated in the presence of NaOD, MeOD and D_2O and an amorphous monobenzylidine derivative (98) as judged by ultraviolet absorption (300 mμ, log ε, 4·73),[77,78] (98 in contrast to 97 gave a negative Zimmerman reaction). These results indicate the presence of one methylene group adjacent to the keto function and consequently limit the site of the hydroxyl in songorine to either C(2) or C(4).

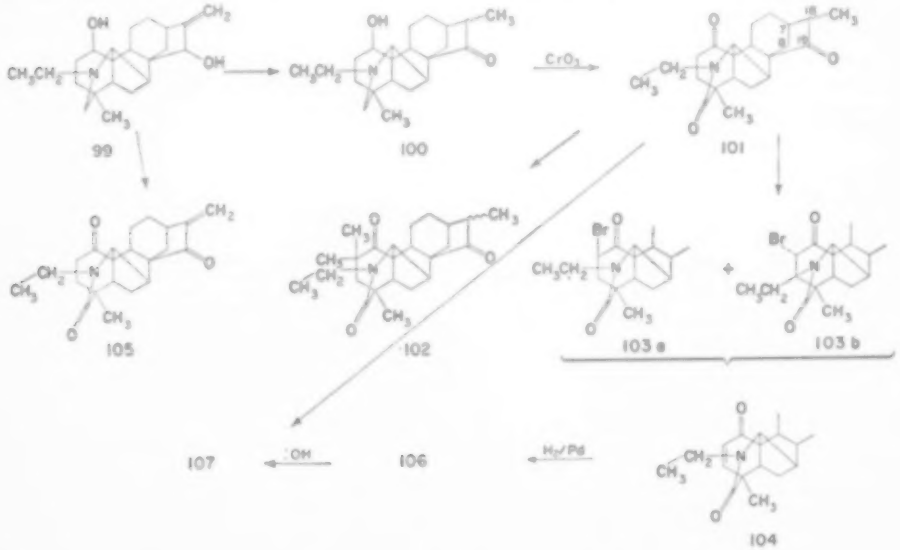
Isodeoxysongorine (100), prepared by isomerization of deoxysongorine (99), on

[73] K. Wiesner, S. Itô and Z. Valenta, *Experientia* **14**, 167 (1958).
[74] E. Ochiai, T. Okamoto, S. Sakai, T. Sugasawa and T. Onouchi, *Chem. & Pharm. Bull.* **7**, 542 (1959).
[75] T. Sugasawa, *Chem. & Pharm. Bull.* In press.
[76] We thank Dr. Sugasawa for giving us manuscripts prior to publication in which these results are presented.
[77] T. Sugasawa, *Chem. & Pharm. Bull.* In press.
[78] The monobenzylidine derivative of cyclohexanone shows absorption at 290 mμ (4·05) while the dibenzylidine derivative shows absorption at 330 mμ (4·40).



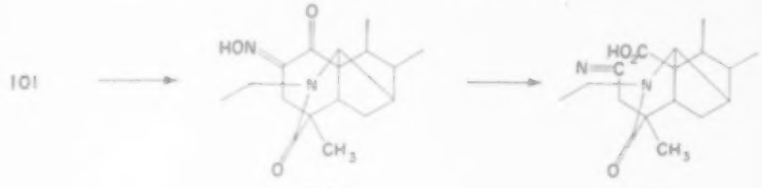
oxidation with chromium trioxide–pyridine gave the diketo lactam, (101), [1733, 1713, 1633 cm^{-1}]. Treatment of the latter with methyl iodide and potassium t-butoxide in t-butanol afforded a gem-dimethyl derivative (102) [1733, 1698, 1638 cm^{-1}] which unlike (101) did not form a benzylidine derivative. Bromination of (101) in glacial acetic acid gave a pair of epimeric ketones [(103a), 317 mμ (2·81); (103b), 299 mμ (2·11)]. Both bromides showed absorption at 1720 cm^{-1}. Dehydrohalogenation of the mixed bromides with lithium chloride in boiling dimethylformamide gave a product (104) with spectral properties characteristic of an α,β-unsaturated ketone in a six-membered or larger ring (1738, 1668, 1638 cm^{-1}). Evidence that bromination had occurred in ring A and not ring D was provided by oxidation of (99) to a neutral product (105) containing the conjugated enone in the five-membered D-ring. [1710, 1725, 1640 cm^{-1}; 233 mμ (4·17); 295 mμ (2·06)].

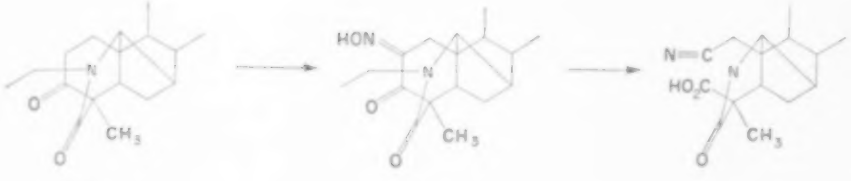
It appears that dehydrohalogenation of (103) in the presence of lithium chloride is accompanied by partial epimerization of the methyl group at C(18), for reduction of



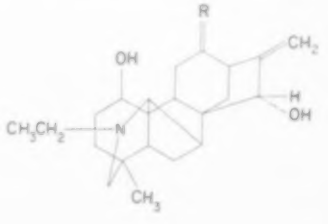
the product (104) over palladium gave a mixture of products [(106), 1733, 1635, 1713 cm^{-1}], which was not identical with (101). However, treatment of both (101) and (106) in methanolic sodium hydroxide gave the same equilibrium mixture of epimers, (107), as judged by the usual criteria.

To ascertain whether the hydroxyl in ring A is situated at C(2) or C(4), the diketolactam (101) was reacted with isoamylnitrite to give the isonitroso derivative (108) and the latter was cleaved with benzenesulfonyl chloride and alkali to the nitrile [(109), 2260 (—C≡N), 2500–2700 (CO_2H), 1730 (CO in 5-ring and CO_2H), 1612, 1630, >N—C=O- - -HO—C=O and >N—C=O]. Since the latter was stable up to its melting point (185°) and did not decarboxylate when boiled in ethanolic hydrogen chloride, it is probable that the keto function in (108) is at C(4). Had it been at C(2), as represented in (110) and (111), the product of the reactions would be the malonamide (112), a type of compound which is known in the ignavine series to decarboxylate easily either when heated to 140–170° or when boiled in the presence of acid.



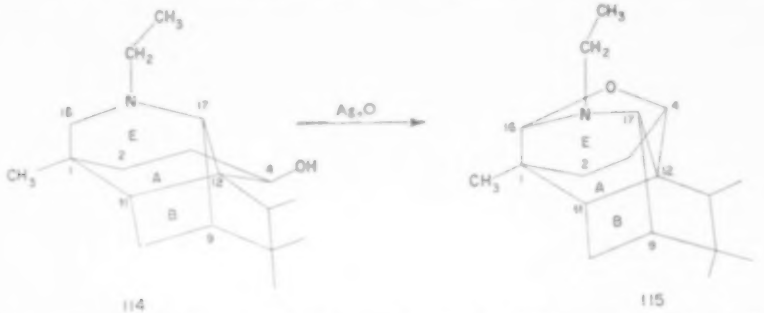


The above transformations led Sugasawa to assign the hydroxyl in ring A to C(4) and therefore songorine may be represented by (113, R = O), while napelline is the



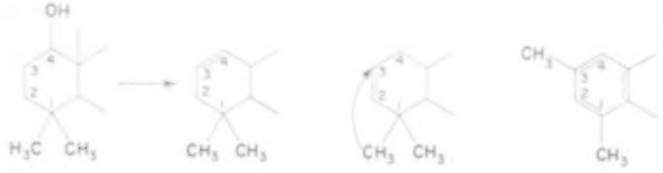
ring C equatorial alcohol (R = - - -OH). In order to be able to form a carbinolamine ether by oxidation of the C(4) hydroxyl, models show that this hydroxyl must be equatorial and that ether formation is accompanied by an inversion of ring A from the chair to boat form as shown in formulas (114–115).

It must be admitted that formation of 1,3,9-trimethyl-7-isopropylphenanthrene by dehydrogenation of isodeoxysongorine (100) hydrochloride is difficult to explain on the basis of structure (113) for songorine. Sugasawa's attempted rationalization



114 115

for the formation of this hydrocarbon assumes that initial cleavage of the C(16)—N bond gives a 1-gem-dimethyl compound. Elimination of the C(4) hydroxyl as water would create unsaturation at C(3)—C(4). Under the drastic conditions of the dehydrogenation, this double bond might migrate to C(2)—C(3). One of the gem-dimethyls might then undergo a rearrangement to the allylic position at C(3). Until further evidence is forthcoming, this scheme must be regarded as purely speculative.



VIII. THE CHEMISTRY OF HETISINE

Hetisine, $C_{20}H_{27}NO_3$, which occurs as a companion of atisine in *Aconitum heterophyllum*, was first isolated by Jacobs and Craig in 1942.[79] The alkaloid represents an unusual structural type and presents a very difficult structural problem both because of its complicated molecular architecture and because of the unusual rearrangements certain of its derivatives undergo.

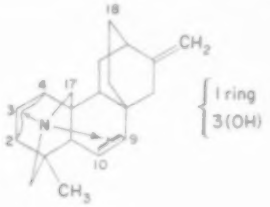
The alkaloid has one double bond which can be hydrogenated,[79] three active hydrogens,[79] a tertiary nitrogen atom and no vicinal hydroxyl groups.[80] N-alkyl and methoxyl determinations are negative.[79] The presence of an exocyclic methylene group is shown by the infrared (3003, 1659, 899 cm^{-1})[81] and NMR spectra (τ = 5·28, 5·46),[62] and confirmed by the isolation of formaldehyde upon ozonolysis.[81] C-methyl determinations and infrared absorption (1379 cm^{-1}) indicate the existence of one C-methyl group in hetisine and two in dihydrohetisine.[42] This is confirmed by the appropriate NMR spectra (τ for C-methyl in hetisine = 9·02).[62] Since the near ultraviolet spectrum of dihydrohetisine is normal,[4] it is clear that hetisine must have a heptacyclic skeleton.

The nature of the oxygen functions is indicated by formation of a crystalline

[79] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **143**, 605 (1942).
[80] W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.* **170**, 189 (1947).
[81] A. J. Solo and S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).

diacetate (3247, 1742, 1252, 1225 cm^{-1}) and an amorphous triacetate, both of which regenerate hetisine on saponification.[42] Furthermore, the alkaloid is inert to both periodate and lead tetraacetate[80] and does not form an acetonide.[42] Thus hetisine possesses three acetylable hydroxyls which are non-vicinal and not in a 1,3-*cis*-diaxial relationship.

Early dehydrogenation studies by Jacobs showed that hetisine gave a complex mixture of hydrocarbons and bases.[80] From the mixture a small amount of the compound identified as pimanthrene was isolated. Recent work utilizing gas phase chromatography to separate the complex dehydrogenation mixture confirms this identification.[62] Since hetisine and atisine are companion alkaloids, one would expect them to be biogenetically and structurally related. While hetisine affords pimanthrene,[62,80] atisine furnishes 1-methyl-6-ethylphenanthrene.[31,32] Dehydrogenation of an isoatisine derivative lacking the secondary allylic hydroxyl, however, gives 1-methyl-6-isopropylphenanthrene,[33] indicating that the presence of the hydroxyl alters the course of the dehydrogenation. Since hetisine gives pimanthrene, it was suspected that the substitution adjacent to the exocyclic methylene group is different than in atisine. The fact that hetisine lacks a free N-alkyl group on the nitrogen[82] and compares in basicity (pK_a' 9·85) with quinuclidine (10·3) suggests a quinuclidine type structure.[62] Models show that only positions 2, 3, 4, 9 and 10 are available for bonding to the nitrogen. The data considered thus far allow one to tentatively deduce skeleton (116) containing one additional ring and three hydroxyl groups. The interest-



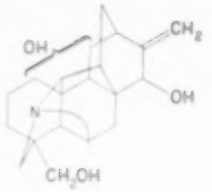
116

ing work on hypognavinol[83] provides an analogy for this kind of skeleton and also suggests bonding for the remaining ring, (see p. 107). The provisional skeleton advanced for hypognavinol on the basis of dehydrogenation data features a norquinuclidine type nitrogen with an extra bridge between C(17) and C(19).

At this point it will be advantageous to consider some of the older Hofmann data of Jacobs[80] since it has an important bearing on certain structural features of hetisine. Hetisine methiodide undergoes a one-stage Hofmann degradation to yield desmethylhetisine. This compound yields starting material when subjected to a second stage Hofmann degradation. Since hetisine has one double bond which can be hydrogenated, one would expect that desmethylhetisine would absorb two moles of hydrogen. However, only a dihydroderivative could be prepared. Dihydrohetisine was also found to undergo a single stage of the Hofmann degradation. The product, desmethyldihydrohetisine, unlike the isomeric dihydrodesmethylhetisine, absorbed one mole of hydrogen. It is evident that the hydrogenable double bond is the newly created one and not the exocyclic methylene. The latter has apparently suffered some kind of change.

[82] This is indicated by the Herzig–Meyer determination and N.M.R. spectrum of hetisine.
[83] S. Sakai, *Chem. & Pharm. Bull.* **6**, 448 (1958).

In an effort to explain these puzzling data, Wiesner proposed structure (117) for hetisine and (118) for desmethylhetisine.[84] To account for disappearance of the double



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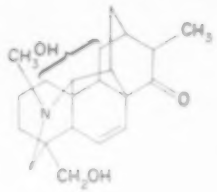
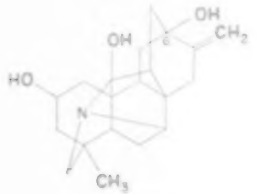


118

bond during the Hofmann degradation, an allylic rearrangement such as is known to occur readily in isoatisine[28] and garryfoline[59] was invoked. However, hetisine is known to have one C-methyl group (I.R., Kuhn–Roth, NMR) and desmethylhetisine shows no carbonyl absorption in the infrared.[42,62] Furthermore, hetisine gives mono- and dicarbonyl derivatives which are not conjugated enones.[42,81] Therefore, it cannot contain the hydroxy methylene and the secondary allylic alcohol shown in (117).

It is clear that the Hofmann data require an allylic rearrangement and therefore one of the hydroxyls must be α- to the $>C{=}CH_2$ group. Since a secondary allylic system is ruled out, the only other site for this hydroxyl is at C(6), i.e. a tertiary allylic alcohol. The remainder of the discussion of hetisine chemistry will be based on formula (119) which has been proposed recently.[81]

The degradations described above may be represented as shown in formulas (120) to (122). Hofmann degradation of hetisine methiodide (120) gives an incipient ketone



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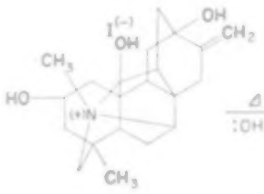

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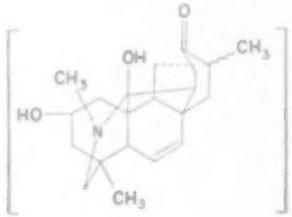

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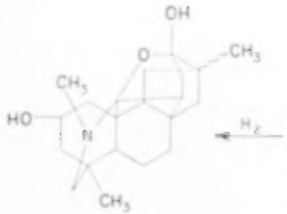

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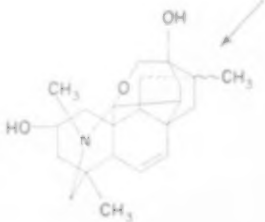
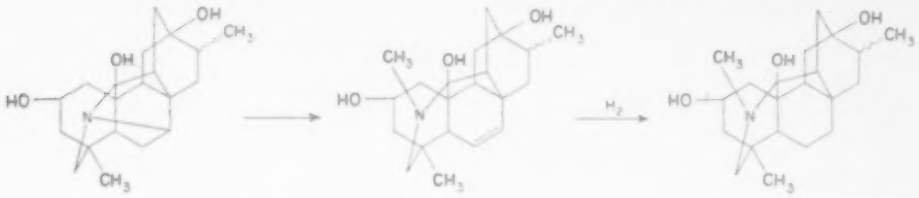


122

(121) which can participate in hemiketal formation with a suitably located hydroxyl on C(17) to give desmethylhetisine (122). The infrared spectrum of the latter shows new bands at 1143 and 1112 cm^{-1} which may be ascribed to the hemiketal. The absorption of one mole of hydrogen by desmethylhetisine is also compatible with

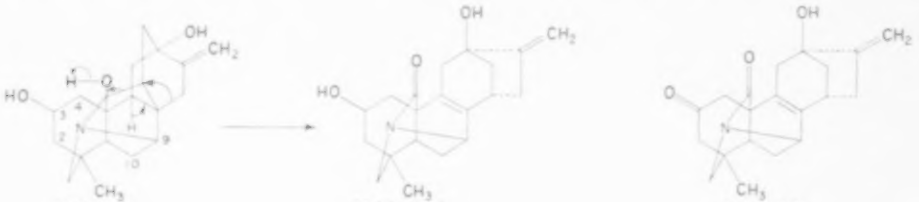
[84] Reference 4, page 62.

structure (122). Dihydrohetisine (124) on the other hand, undergoes a normal Hofmann degradation to give a product (125) absorbing one mole of hydrogen to give (126).



124 125 126

Evidence for the location of an oxygen atom at C(17) in hetisine follows from oxidation experiments with chromium trioxide in pyridine.[42] The products formulated in (127) and (128) are bicyclic lactams possessing a bridgehead nitrogen and arise from a skeletal rearrangement. Hydrolysis of (127) and (128) in base gave the respective amino carboxylates (1575 cm^{-1}).[81] Since this kind of system is incapable of resonance on

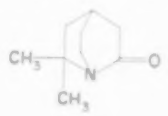


Hetisine

127: 3300, 3106, 1718, 1652 (w), 883 cm^{-1}

128: 3106, 1718, 1653 (w), 892 cm^{-1}

theoretical grounds, it would be expected to have properties of an aminoketone rather than of a lactam. In agreement with this, these compounds are basic (pK_a' 8·1, 6·7 respectively), form stable hydrochlorides and methiodides, and show ketonic rather than lactam absorption in the infrared (1718 cm^{-1}). The first simple example of such a system is 2,2-dimethyl quinuclidone-6 (129) which is basic (pK_a' 5·33), forms a hydrochloride and shows carbonyl absorption characteristic of a ketone (1733) rather than a lactam.[85,86] A comparison of the carbonyl absorption of (127) and (128) with that of 2,2-dimethyl quinuclidone-6 (1733 cm^{-1}) is the basis of the assignment of



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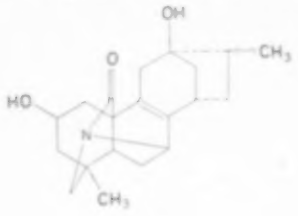
an N—C(9) bond (bicyclo-2,2,2 system) rather than a N—C(10), N—C(2) or N—C(3) bond (bicyclo-2,2,1 system) in hetisine. The latter system would be expected to show absorption in the region of a cyclopentanone.

Some evidence for the course of this unusual oxidation is available from a study

[85] H. Pracejus, *Chem. Ber.* 988 (1959).

[86] Wildman *et al.* [*J. Amer. Chem. Soc.* **80**, 2590 (1958); *Ibid.* **81**, 197 (1960)] have described a series of alkaloid oxidation products containing a quinuclidone-2 conjugated with an aromatic ring. Here too, the infrared absorption is characteristic of a cyclohexanone (conjugated with the phenyl ring).

of (128). It absorbs two moles of hydrogen to give a tetrahydro derivative (130) which shows the presence of two active hydrogens, a diminished carbonyl peak at 1704 cm^{-1} and no exocyclic methylene absorption. Furthermore, NMR data indicate the absence



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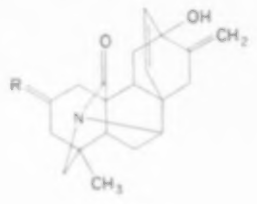
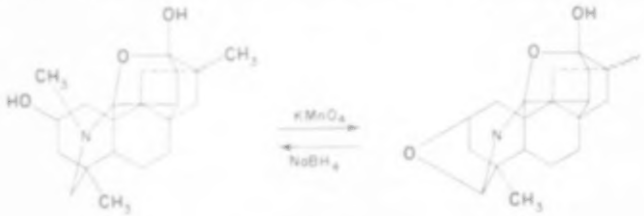


131 R = OH
R = O

of a hydrogen atom on the double bond.[62] These data rule out structure (131) which was originally suggested for these bicyclic lactams.[81,86a] It must be emphasized that though the structures proposed for these bicyclic lactams are in accord with the properties observed thus far, they are to be regarded as tentative.

Oxidation of dihydro-desmethylhetisine (123) with permanganate gave a crystalline product, $C_{21}H_{29}NO_3$, which shows weak hydroxyl absorption, but no carbonyl absorption in the infrared. Reduction with sodium borohydride regenerates starting material. The oxidation product is represented as a carbinolamine ether (132). The spectrum of the latter shows absorption at 1153, 1143, 1124 and 1103 cm^{-1} which is attributed to O—C—O and O—C—N linkages. Analogy for this type of reaction is seen in the oxidation of desmethylhypognavinol with alkaline ferricyanide and dihydronapelline with silver acetate to carbinolamine ethers.[73,83,102] The third hydroxyl group is located tentatively at C(3) rather than C(4) because of the stability of the

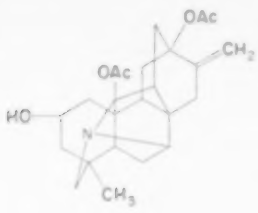


123 132

hydrolysis product from the keto-bridgehead lactam (128) [amino keto carboxylate]. If at C(4), the hydrolysis product would be a β-keto carboxylate and hence thermally unstable.

The acetylation products of hetisine require comment. The diacetate is represented as a ditertiary acetate (133) since on oxidation it furnishes a ketodiacetate (134) which may be saponified to give the parent dihydroxy ketone (1716 cm^{-1}; oxime). It may appear strange that two tertiary hydroxyls are acetylated in preference to a secondary hydroxyl. However, because of the bridgehead positions, the tertiary hydroxyls are relatively accessible, whereas the secondary hydroxyl is β-axial and can hydrogen bond to the nitrogen in such a way as to make acetylation difficult.

[86a] Structures 127 and 128 were first suggested on mechanistic grounds by Prof. Gilbert Stork. (Private communication).



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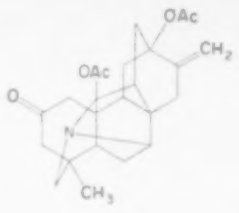

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IX. THE CHEMISTRY OF IGNAVINE, HYPOGNAVINE AND KOBUSINE

In recent years a wide range of *Aconitum* species native to Japan have been examined for alkaloids. Among those encountered are three, ignavine, hypognavine and kobusine which have been the subject of considerable investigation and now appear to have the same skeleton. Since most of the chemistry of these compounds has been published within the past three years, they will be covered in some detail.

A. *Ignavine*

From the root nodules of *Aconitum sanyoense* Nakai[87], *A. tasiromontanum* Nakai[87,88] and *A. japonicum*,[89] the Ochiai school has isolated several toxic ester alkaloids and a simple-type alkaloid named ignavine. Early studies showed that ignavine, $C_{27}H_{31}NO_6$, does not contain a methoxyl, methylenedioxy, or an N-methyl group and is unreactive toward the usual carbonyl reagents. Hydrogenation with a palladium–charcoal catalyst gave a dihydroderivative. Saponification of ignavine with methanolic potassium hydroxide gives one mole of benzoic acid and an alkamine, designated as anhydroignavinol, $C_{20}H_{25}NO_4$, m.p. 302°. Methiodide formation is also accompanied by the loss of a mole of water from ignavine.[87]

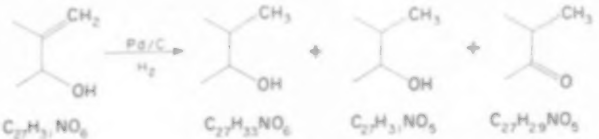
Of the six oxygens in ignavine, two occur in the benzoyloxy group and four in hydroxyls. One of these hydroxyls is on a carbon α- to that bearing the benzoyloxy group as shown by the fact that the hydrolysis product is susceptible to periodate cleavage while ignavine is not.[87] Two of the hydroxyls are acylable as is shown by the preparation of mon- and di-benzoates, di-*p*-bromobenzoates and di-*p*-nitrobenzoates.[90] These acyl derivatives are all characterized by the fact that they contain a mole of water less than would be calculated on the basis of ignavine and thus are anhydroignavinol derivatives. Saponification of these derivatives affords anhydroignavinol. It is thus evident that ignavine contains an unusual hydroxyl which on methiodide formation or acylation is eliminated as water. Early evidence was interpreted in favor of double bond formation, but recent studies favor ether formation accompanying dehydration.

Hofmann degradation of the methiodide of anhydroignavinol gives a des-N-methyl derivative, $C_{21}H_{27}NO_4$, m.p. 265–267°, which is reported to absorb one mole of hydrogen when reduced in methanol over Pd, Pt/C[90] and two moles over platinum in acetic acid.[91] Application of the Hofmann degradation to the methiodide of the

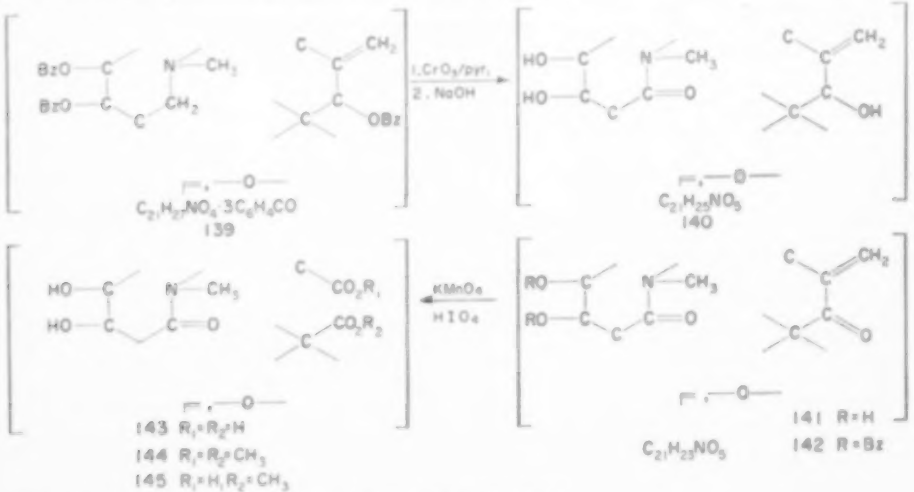
[87] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani and H. S. Hai, *J. Pharm. Soc. Japan* **27**, 816 (1952).
[88] E. Ochiai, T. Okamoto, T. Sugasawa and H. Tani, *J. Pharm. Soc. Japan* **27**, 1605 (1952).
[89] E. Ochiai, T. Okamoto, S. Sakai, M. Kaneko, K. Fujisawa, U. Nagai and H. Tani, *J. Pharm. Soc. Japan* **76**, 550 (1956).
[90] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani, S. Sakai, H. S. Hai and H. Endo, *Pharm. Bull.* **1**, 60 (1953).
[91] E. Ochiai and T. Okamoto, *Chem. & Pharm. Bull.* **7**, 556 (1959).

des-N-base regenerated des-N-methylanhydroignavinol. Failure to carry the Hofmann reaction through a second stage is reminiscent of the behavior encountered with des-N-methylhetisine.[90]

The presence of an exocyclic methyl group in anhydroignavine was indicated by the infrared spectrum (1645 and 892 cm^{-1}) and by the formation of formaldehyde on ozonization.[90] Careful study of the hydrogenation of ignavine (135) over palladized charcoal has resulted in the isolation of three different products, dihydroignavine (136), $C_{27}H_{33}NO_6$, m.p. 173°, anhydrodihydroignavine (137), $C_{27}H_{31}NO_5$, m.p. 236° and a compound assumed to be a cyclohexanone (1692 cm^{-1}), anhydrodihydroignavinone (138), $C_{27}H_{29}NO_5$, m.p. 260°. Formation of the latter two compounds involved the loss of a mole of water during hydrogenation. The appearance of a ketone (1692 cm^{-1}) among the hydrogenation products of a terminal methylene group is typical of the behavior of hypognavine[97] and kobusine[109] and involves rearrangement of an allyl alcohol system to a methyl ketone. These reactions confirm the presence of a secondary allyl alcohol system in ignavine.[92]



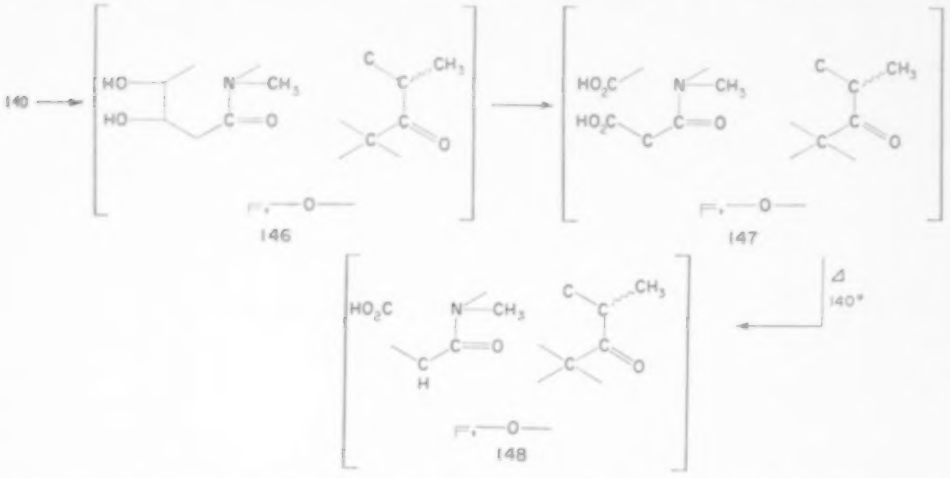
Further operations on the secondary allylic system were carried out utilizing des-N-methylanhydroignavinol tribenzoate (139) as a substrate.[92] Oxidation of (139) with chromium trioxide–pyridine gave a lactam tribenzoate (1645 cm^{-1}; δ-lactam) which on saponification afforded the parent δ-lactam (140) [1615 cm^{-1}]. Further oxidation of the latter with chromium trioxide–pyridine furnished an α,β-unsaturated ketone (141) with absorption bands characteristic of the conjugated enone (1615, 1687 cm^{-1}) and δ-lactam (1590 cm^{-1}). Oxidation of the dibenzoate (142) with permanganate–periodate followed by hydrolysis furnished a dicarboxylic acid (143),



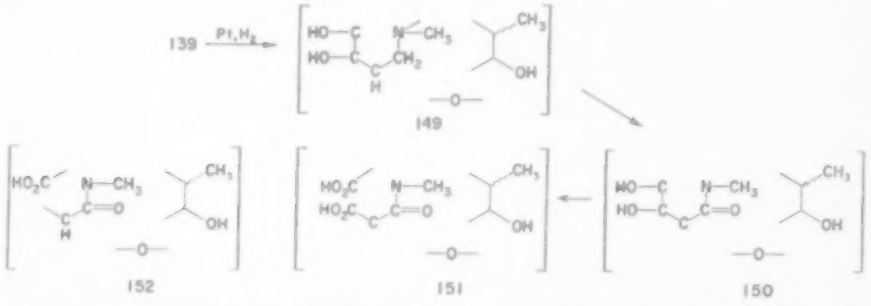
[92] E. Ochiai, and T. Okamoto, *Chem. & Pharm. Bull.* **7**, 550 (1959).

(1690, 1708, 1585 cm^{-1}). Saponification of dimethylester (144) gave a mono-methyl ester (145) indicating one of the carboxyls in (143) is tertiary.[92]

The presence of a glycol system in (140) was demonstrated by cleavage to dicarboxylic acid (147). The exocyclic methylene group of (140) was rendered immune to oxidation by acid catalyzed rearrangement to the methyl ketone (146) (1700 cm^{-1}). Treatment with permanganate gave an amorphous dicarboxylic acid (147) which eliminated CO_2 at 140°. A parallel series of reactions was also carried out on one of



the isomeric tetrahydroderivatives (149) obtained when des-N-methylanhydrohypognavinol (139) was hydrogenated over platinum. Oxidation of (149) as the tribenzoate followed by saponification gave the δ-lactam (150). Further oxidation with perman-

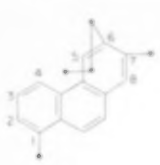


ganate gave an amorphous dicarboxylic acid (151) [1708 cm^{-1}, 1637 cm^{-1}], which again lost carbon dioxide at low temperature (140–170°) to give a monocarboxylic acid 152, (1712, 1620 cm^{-1}). The facile elimination of carbon dioxide suggests the presence of a malonamide moiety in acids (148) and (151) and supports the partial structure about the nitrogen atom as represented in the above formulas.[92]

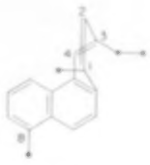
Careful selenium dehydrogenation experiments on anhydroignavinol have yielded four alkyl phenanthrenes as well as alkyl benzenes and naphthalenes.[93] Two of the alkylphenanthrenes are crystalline: a $C_{19}H_{20}$ hydrocarbon, m.p. 82–84°, picrate,

[93] E. Ochiai, T. Okamoto, T. Sugasawa and S. Sakai, *Pharm. Bull. Japan* **2**, 388 (1954).

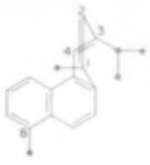
142°, TNB, 156° and a $C_{19}H_{20}$ or $C_{19}H_{18}$ hydrocarbon, m.p. 145–147°, picrate 135°, TNB, 160°. The two liquid phenanthrenes have picrates of m.p. 173–175° and 175–177°. It is a tribute to the patient and meticulous work of the Japanese workers that three of the four hydrocarbons have been recently identified by synthesis. The 82–84° hydrocarbon is 1,7-dimethyl-6-n-propylphenanthrene (153),[94] the liquid with the picrate melting at 173–175° is a 1,8-dimethyl-3-ethylphenanthrene (154)[95] and the one with the picrate melting at 175–177° is 1,8-dimethyl-3-isopropylphenanthrene (155).[95] These products account for nineteen of the twenty carbon atoms of anhydroignavinol.



153



154



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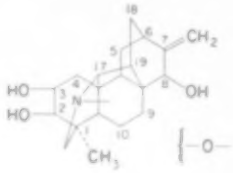


156

In view of the diterpenoid nature of the aconitum alkaloids and the demonstrated presence of an allylic alcohol system in ignavine, it is reasonable to assume the alkaloid contains a bicyclo-2,2,2-octane-allyl alcohol system such as occurs in atisine and which is shown in (156). This is given further credence by the oxidation of des-N-methyl-oxo-anhydroignavinol (140) to a dicarboxylic acid (143) in which one of the carboxyls is tertiary.[92] The dehydrogenation products (153, 154, 155) suggest a bond between C(19) and C(17) and a methyl group at C(1). Considering the partial structure involving the nitrogen which was deduced above, and the analogy to other diterpene alkaloids, one may place the nitrogen between C(16) and C(17) and hydroxyls at C(2) and C(3). Since ignavine shows no N-alkyl group, it is evident that a third bond must extend from nitrogen to one of the rings. The Japanese authors select C(10) as the most likely site. The remainder of anhydroignavine chemistry will be discussed on the basis of formula (157).

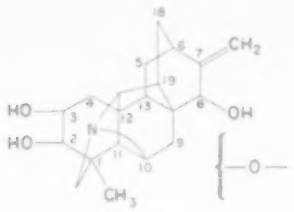
The fact that anhydroignavinol consumes one mole of periodic acid in two hours whereas ignavine is resistant to the reagent suggests that the α-glycol system which is present in anhydroignavinol is masked by the benzoyloxy group in ignavine. Oxidation of ignavine with chromium trioxide–pyridine gives a mixture of mono- and diketones. The diketone showed bands at 1708 and 1630 for the conjugated enone system and also bands assignable to a ketol benzoate at 1740 and 1722 cm^{-1}. Saponification gave a ketol as indicated by its behavior toward Tollins reagent and triphenyltetrazolium chloride. Location of the benzoyloxy group at C(2) rather than C(3) is suggested by the positive Zimmerman reaction given by the ketobenzoate.[91]

The published data clarify the nature of four of the six oxygens of ignavine and three of the four of anhydroignavinol. The fourth oxygen in anhydroignavinol is thought to exist as an ether since no hydroxyl band is observable in the infrared spectra of tribenzoyl anhydroignavinol, tribenzoyl-des-N-methylanhydroignavinol

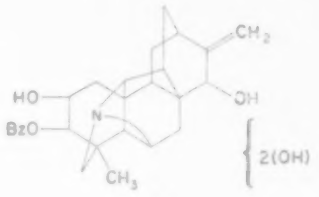
[94] E. Ochiai, T. Okamoto, S. Hara, S. Sakai and M. Natsume, *Chem. & Pharm. Bull.* **6**, 327 (1958).

[95] Personal communication from Prof. T. Okamoto. The author cordially thanks Prof. Okamoto for placing a manuscript by S. Hara and Y. Tokushige at his disposal which describes the synthesis of the two oily hydrocarbons. The pure synthetic hydrocarbons show the following constants: (154), m.p. 52–53°, TNB, m.p. 176–177·5°, picrate, 161–162°; (155), m.p. 74–76°, TNB, m.p. 182–183°, picrate, m.p. 162–163°. *Note added in proof:* The work cited has since been published in *Chem. & Pharm. Bull.* **8**, 976 (1960).

and tribenzoyl-des-N-methyl-oxo-anhydroignavinol. It is therefore probable that the loss of water accompanying many of the reactions of ignavine, e.g. saponification, reduction, acylation, involves *ether* rather than double bond formation. Possible positions for the hydroxyls involved in the elimination assuming a β-glycol moiety are, C(5–18), C(9–19), C(9–13) and C(11–13). Since ignavine has a normal pK_a' value (7·7) for a tertiary amine, it seems unlikely hydroxyls could be at C(17) or C(16). In view of the above, anhydroignavinol and ignavine have been represented by partial structures (157) and (158) respectively.[91]



157



158

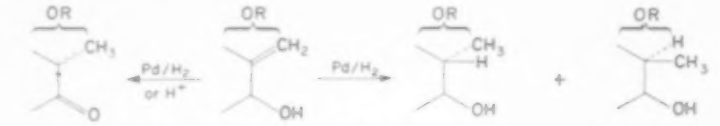
B. *Hypognavine*

Certain varieties of *Aconitum sanyoense* have been shown to contain an ester alkaloid called hypognavine which contains one less oxygen atom than ignavine and is in many respects similar to it.[96] Thus hypognavine, $C_{27}H_{31}NO_5$, is a benzoyl ester, has no methoxyl or N-methyl group, fails to react with the usual carbonyl-test reagents and contains one hydrogenable double bond. Like ignavine, it has two acylable hydroxyls and an exocyclic methylene group (1666, 895 cm^{-1}, ozonization gives formaldehyde).[96,97] However, in contrast to ignavine, hypognavine may be saponified to give an alkamine (hypognavinol, $C_{20}H_{27}NO_4$) without loss of a mole of water. Acylation reactions and methiodide formation are also straightforward in the case of hypognavine.[96]

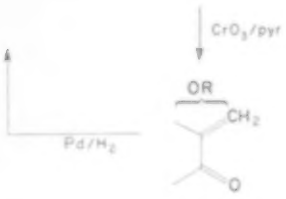
The exocyclic methylene group in hypognavinol manifests the same characteristics as that in songorine and ignavine, namely partial rearrangement to a methyl ketone on catalytic hydrogenation with palladium charcoal or treatment with acids.[97] Thus hydrogenation of hypognavine (159) gave a mixture from which three products were isolated: dihydrohypognavine (160), m.p. 235°, allodihydrohypognavine (161), m.p. 252° and dihydrohypognavinone (162), m.p. 296° (1704, 1689 cm^{-1}). The latter was also obtained from hypognavine in small yield by heating with aqueous 10 per cent sulfuric acid. The alkamines corresponding to these hydrogenation products were obtained by alkaline saponification and can be designated as dihydrohypognavinol (160a), m.p. 302°, allodihydrohypognavinol (161a), m.p. 270°, and dihydrohypognavinolone (162a), m.p. (·HBr) 348° (1712 sh, 1701 cm^{-1}). The vinyl band at 895 cm^{-1} was absent in all the above products. Hypognavine was oxidized to an α,β-unsaturated ketone (163) in 30 per cent yield with manganese dioxide and 70 per cent yield with chromium trioxide–pyridine. The product, hypognavinone, showed absorption typical of the benzoyl group (1709, 1600, 1580 cm^{-1}) and conjugated enone [1705, 1630 cm^{-1}; λ_{max} 231 (4·35)] and when reduced with palladium charcoal

[96] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani and S. Sakai, *Pharm. Bull. Japan* **1**, 152 (1953).
[97] S. Sakai, *J. Pharm. Soc. Japan* **76**, 1436 (1956).

gave the known dihydrohypognavinone (162). These reactions[98] afford clear evidence for the existence of a secondary allyl alcohol system such as occurs in atisine,[25,38] ignavine,[92] and songorine.[70]

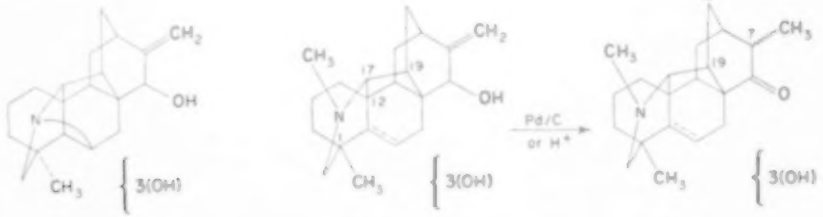


162 R = Bz
162a R = H
159 R = Bz
159a R = H
160 R = Bz
160a R = H
161 R = Bz
161a R = H



163

Selenium dehydrogenation of the alkamine hypognavinol gives a small amount of 1,8-dimethyl phenanthrene,[97] 1,7-dimethyl-6-n-propyl phenanthrene[94] and 1,8-dimethyl-3-ethyl phenanthrene,[99] the latter two being characteristic products also obtained from anhydroignavinol.[95] In addition a weakly basic fraction was obtained in small yield with a ultraviolet spectrum in some respects similar to that of 3-azaphenanthrene.[100] It is therefore likely that hypognavine has the same general type of diterpene alkaloid skeleton as that derived for ignavine. The formula (164) will be used as a basis for interpreting other reactions of hypognavinol. The alternate structure with a N—C(3) bond is less probable because it does not easily explain oxidation data obtained with dihydrohypognavinone and des-N-methylhypognavinol (*vide infra*).



164 165 166

Hofmann degradation of the methiodide of hypognavinol gave a des base (165),

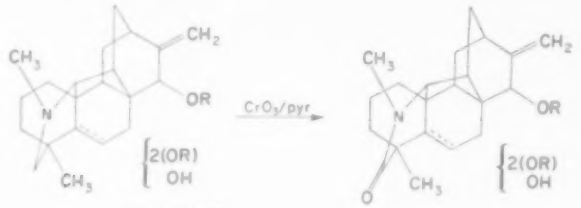
[98] The indicated configuration of the methyl groups is purely arbitrary. It is interesting to note that the ketobase hydrobromide, m.p. 346°, obtained by catalytic reduction of hypognavinol (159a) is not identical with the dihydrohypognavinolone hydrobromide (162a) obtained by catalytic reduction of hypognavine and subsequent saponification. The nonidentity is probably due to the difference in configuration of the newly formed methyl group.

[99] The author gratefully acknowledges receipt of this unpublished information from Professor Okamoto. See footnote 95.

[100] S. Sakai, *Chem. & Pharm. Bull.* **6**, 448 (1958).

in 70% yield and a by-product, m.p. 225°, which has been identified as a des-N-methyldihydrohypognavinolone (166).[100,101] Des-N-methylhypognavinol on treatment with palladium–charcoal or acid undergoes an allylic rearrangement to give two isomeric methyl ketones, one of which is identical with the Hofmann by-product (166). The resistance of des-N-methylhypognavinol toward a second Hofmann degradation is well accommodated by structure (165), for the β-positions to nitrogen at C(1) and C(12) carry no hydrogen and formation of a C(17)—C(19) double bond would violate Bredt's Rule.

The size of the heterocyclic ring in (164) is indicated by oxidation of triacyl des-N-methylhypognavinol derivatives (167) to δ-lactams.[102] Thus oxidation of tribenzoyl and tri-*p*-nitrobenzoyl hypognavinol gave lactams (168) with amide absorption at 1656 and 1630 cm^{-1} respectively. A similar oxidation of the triacetyl-des-N-ethyl-hypognavinol gave a lactam showing absorption at 1635 cm^{-1}. Saponification of the latter gave a product with amide absorption at 1614 cm^{-1}. All these values are within the range characteristic of δ-lactams.[103]

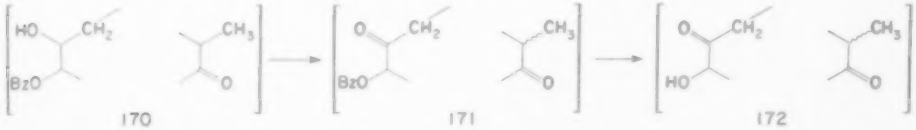


R = C_6H_5CO

167 R = p—NO_2—C_6H_5CO 168

The three remaining oxygen atoms of hypognavinol exist as hydroxyl groups of which two are acylable. The nonacylable hydroxyl is tertiary since tribenzoyl hypognavinol (dibenzoylhypognavine) can be recovered unchanged from oxidation with chromium trioxide–pyridine. Oxidation of dihydrohypognavinone (170) under the same conditions gives a diketoester (171) which has a methylene group adjacent to the newly created carbonyl. (Zimmerman color reaction.) Saponification of the diketoester gave a pair of epimeric diketoalkamines (172) which undergo the usual reducing reactions for α-ketols and in contrast to the diketoester (171) consume one mole of periodic acid. It is thus clear that the new carbonyl group together with the benzoyloxy group comprises an α-ketol ester.[101]

The location of this α-glycol system in ring A of the hypognavinol skeleton is provided by the following data. Oxidation of des-N-methylhypognavinol (167) with silver oxide in ether or alkaline ferricyanide affords a crystalline carbinolamine ether



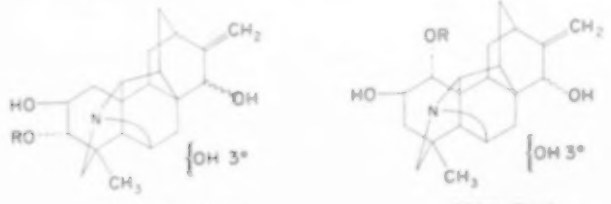
170 171 172

[101] S. Sakai, *Chem. & Pharm. Bull.* 7, 50 (1959).
[102] S. Sakai, *Chem. & Pharm. Bull.* 7, 55 (1959).
[103] Treatment of 169 for two hours with 50 per cent sulfuric acid at 135° gave no detectable acetic acid. Hence, the band at 1614 cm^{-1} is due to lactam absorption and not an N-acetyl group.

(174), $C_{21}H_{27}NO_4$, pK_a' 5·33, from which the starting material may be regenerated by reduction with sodium borohydride. Salts (175) of the carbinolamine ether show infrared absorption typical of the $>C=\overset{+}{N}<$ group (1686–1679 cm^{-1}) and regenerate the parent base on treatment with alkali. Acetylation of the perchlorate of (175) gives a triacetate (176) with a pK_a' of 10·5 (50 per cent cellosolve). The Japanese workers explain the formation of a carbinolamine ether by assuming that oxidation proceeds initially at C(16) [or C(17)] to give 173. Subsequent elimination of water between the hydroxyl and a properly disposed neighboring hydroxyl would give the required ether. Models show that an axial hydroxyl at C(3) is most favorable for this closure. Moreover, it is to be noted that oxidation at C(17) is unlikely since the open form (salt) of

this carbinolamine ether (177) would violate Bredt's Rule. These transformations parallel the formation of the carbinolamine ether from des-N-methylhetisine and songorine and have been represented as involving an axial 3-hydroxyl group and the C(16) methylene group as illustrated.[100,102]

The question of whether the second hydroxyl of the glycol system is at C(2) or C(4) has not been settled. Since the diketoalkamines (172) consume one mole of periodate in twenty hours whereas hypognavinol and des-N-methylhypognavinol (167) require several hundred hours for the consumption of a mole of periodate or tetraacetate, it was inferred that a *trans*-glycol system is present. The benzoyloxy group in hypognavine was accordingly assigned a 2-α or 4-α configuration. The site of the tertiary hydroxyl is unknown. Hypognavine is thus represented by structure (179a) or (179b) and hypognavinol by (178a) or (178b).[102]



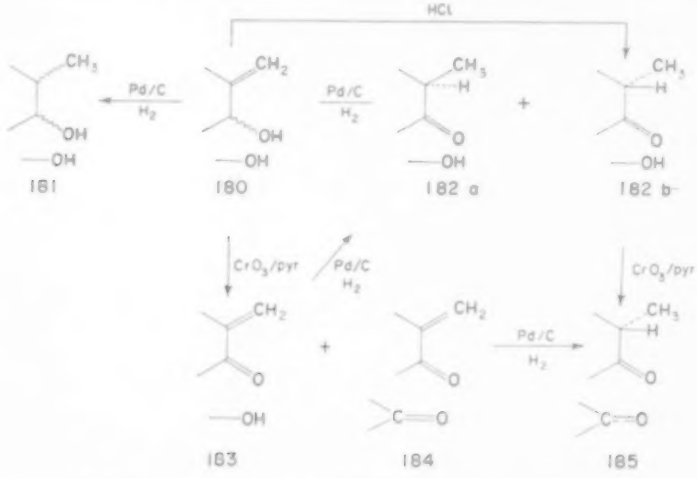
178 a, R = H
179 a, R = COC_6H_5

178 b, R = H
179 b, R = COC_6H_5

C. *Kobusine*

Though twenty years have elapsed since kobusine, $C_{20}H_{27}NO_2$, was first isolated from *Aconitum sachalinense* Fr. Schmidt by Singinome,[104,105] its structure has only recently begun to be clarified. In the early work one oxygen was shown to exist as a hydroxyl and the other thought to be in an ether linkage. The presence of one double bond was shown by hydrogenation.[108] Subsequent work by the Okamoto school has revealed many similarities between the chemistry of kobusine and ignavine and hypognavine and allowed the skeleton to be derived with reasonable certainty.[109,110]

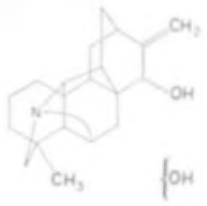
The later work has demonstrated the presence in kobusine of a secondary allyl alcohol moiety (180) (1648, 888 cm^{-1}) such as is common to atisine, ignavine and hypognavine. Thus reduction over palladium–charcoal gave dihydrokobusine (181) and two isomeric ketones, α-dihydrokobusinone (182a) and β-dihydrokobusinone (182b) which result from rearrangement of the allyl alcohol system. Spectral properties were in accord with a ketone in a six-membered ring (1705 cm^{-1}). The β-dihydrokobusinone could be obtained from the α-isomer or from kobusine itself by treatment with 5 per cent hydrochloric acid. Oxidation of kobusine with chromium trioxide–pyridine gave a monoketoalcohol, kobusinone (183) (3100, 1692, 1632 cm^{-1}) and a diketone, ketokobusinone (184) (1721, 1708, 1628 cm^{-1}) both of which compounds are α,β-unsaturated ketones. Catalytic hydrogenation of ketokobusinone gave a saturated diketone (185) (1707 cm^{-1}) which was identified with the product obtained by oxidation of β-dihydrokobusinone. A similar hydrogenation of kobusinone (183) gave α-dihydrokobusinone (182a). It is rather interesting that ketokobusinone (184) gave a compound with the configuration of the methyl group epimeric



[104] H. Suginome and F. Shimanouchi, *Liebigs Ann.* **545**, 220 (1940).
[105] Kobusine has also been isolated from *A. luciduculum*[106,107] and *A. sachalinense*.[107]
[106] H. Suginome, S. Kakumoto and J. Sonoda, *J. Fac. Sci., Hokkaido Univ.* (*Ser. III, Chem.*) **4**, 25 (1950); *Chem. Abstr.* **46**, 1007 (1952).
[107] H. Suginome and S. Imato, *J. Fac. Sci., Hokkaido Univ.* (*Ser. III, Chem.*) **4**, 33 (1950); *Chem. Abstr.* **46**, 1008 (1952).
[108] H. Suginome and S. Umezawa, *J. Fac. Sci., Hokkaido Univ.* (*Ser. III, Chem.*) **4**, 15 (1950); *Chem. Abstr.* **46**, 1007 (1952).
[109] T. Okamoto, *Chem. & Pharm. Bull.* **7**, 44 (1959).
[110] M. Natsume, *Chem. & Pharm. Bull.* **7**, 539 (1959).

to that obtained from kobusinone. The above reactions demonstrate that kobusine contains a CH_2—C—C—OH group and another secondary hydroxyl in a six- or larger-membered ring.[109]

Selenium dehydrogenation of kobusine gives 1,7-dimethyl-6-n-propylphenanthrene, the characteristic product of anhydroignavinol[94] and hypognavinol[94] and two aromatic bases which have not yet been identified. On the basis of the isolation of 1,7-dimethyl-6-n-propylphenanthrene and by analogy with ignavine and hypognavine, it is reasonable to suppose that kobusine is modeled on the same skeleton. Only one hydroxyl remains to be located and the partial structure of kobusine may be represented by (186).[110]



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SUR LA GEISSOSPERMINE

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(*Received* 19 *December* 1960)

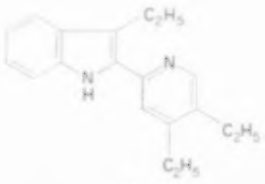
Abstract—La geissospermine $C_{40}H_{44}O_2N_4$ peut être scindée en milieu acide en geissoschizine $C_{21}H_{24}O_2N_2$ et geissoschizoline $C_{19}H_{25}ON_2$, dans certaines conditions on obtient de plus l'apogeissoschizine $C_{21}H_{22}O_2N_2$. Des formules structurales sont proposées pour ces trois produits et des arguments expérimentaux permetten d'attribuer à la geissospermine la formule I.

LA geissospermine, découverte en 1877 par Hesse,[1,2] est le principal alcaloïde du *Geissospermum laeve* (Vellozo) Baillon, apocynacée brésilienne connue depuis longtemps en thérapeutique, comme fé'brifuge, sous le nom de paõ pereira.

Bertho avec différents collaborateurs[3–5] s'est depuis 1931 intéressé aux problèmes posés par la formule et la structure de cet alcaloïde et Wiesner, Rideout et Manson ont en 1953[6] publié une note intéressante concernant les mêmes sujets.

I

geissospermine



II

alstyrine

[1] O. Hesse, *Ber. Dtsch. Chem. Ges.* **10**, 2162 (1877).
[2] O. Hesse, *Ann. Chem.* **202**, 141 (1880).
[3] A. Bertho et G. von Schuckmann, *Ber. Dtsch. Chem. Ges.* **64**, 2278 (1931).
[4] A. Bertho et F. Moog, *Ann. Chem.* **509**, 241 (1934).
[5] A. Bertho et H. F. Sarx, *Ann. Chem.* **556**, 22 (1944).
[6] K. Wiesner, W. Rideout, J. A. Manson, *Experientia* **9**, 369 (1953).

La conclusion essentielle de ces travaux est que la geissospermine résulte de l'union de deux parties qui peuvent être séparées par hydrolyse acide.

Au cours des trois dernières années, les recherches simultanées et indépendantes de Rapoport et de ses collaborateurs[7-9] et celles du groupe de la Faculté de Pharmacie de Paris (Le Hir et Puisieux, Le Men et Lévy, et Goutarel*[10-14]) ont abouti tout récemment[15] à proposer pour la geissospermine la formule structurale I dont la justification fait l'objet de la présente mise au point.

La geissospermine (F = 213–214°, $(\alpha)_D^{20°}$ −101° (éthanol) correspond à la formule $C_{40}H_{48}O_3N_4$; définitivement acceptée depuis l'étude des produits d'hydrolyse.

Dans l'acide chlorhydrique 2 N, la geissospermine se scinde en *geissoschizine* et en *geissoschizoline*[10,16]

$$\underset{\text{geissospermine}}{C_{40}H_{48}O_3N_4} + H_2O \underset{CH_3COOH,\ 10\%}{\overset{HCl\,2N}{\rightleftharpoons}} \underset{\text{geissoschizine}}{C_{21}H_{24}O_3N_2} + \underset{\text{geissoschizoline}}{C_{19}H_{26}ON_2}$$

Dans l'acide chlorhydrique concentré, la geissoschizine est partiellement remplacée par un produit de deshydratation: *l'apogeissoschizine*.[7]

Dans l'acide acétique à 10%, on observe au contraire une condensation de la geissoschizine et de la geissoschizoline redonnant partiellement de la geissospermine.[12]

Comme on le verra plus loin, il a été également possible de réaliser directement la deshydratation de la geissoschizine en apogeissoschizine[15] et inversement le passage de l'apogeissoschizine á la geissoschizine.[16]

A. STRUCTURE DE LA GEISSOSCHIZINE

La *geissoschizine*, (F = 194–196°, $(\alpha)_D^{21}$ +115° (éthanol) répond à la formule $C_{21}H_{24}O_3N_2$. Elle possède un groupement méthoxyle et deux atomes d'hydrogène actifs, un seul groupement $C{-}CH_3$. L'oxydation chromique par la méthode de Kuhn–Roth ne fournit que de l'acide acétique qui peut être caractérisé par la méthode complétée[17b] de Bickel, Schmid et Karrer[17]. L'ozonolyse provoque la formation d'acétaldehyde.[8] On en déduit la présence dans la geissoschizine d'une chaine éthylidène.

Des trois atomes d'oxygène présents dans la molécule, l'un appartient à une fonction aldéhyde et les deux autres à un groupement carbométhoxyle.

La fonction aldéhyde est mise en évidence par la formation d'une dinitro-2-4 phénylhydrazone, isolée sous forme de chlorhydrate $C_{27}H_{28}O_6N_6$, HCl; (F = 198°) et par la réaction de Tollens qui est nettement positive.

La fonction ester carboxylique est révélée par la présence d'une bande d'absorption à 1720 cm^{-1} dans le spectre I.R. du chlorhydrate de dinitro 2-4 phénylhydrazone.

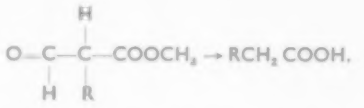
* Auxquels j'adresse ici mes remerciements très sincères.

[7] H. Rapoport, T. P. Onak, N. A. Hughes et M. G. Reinecke, *J. Amer. Chem. Soc.* **80**, 1601 (1958).
[8] H. Rapoport, R. J. Windgassen, N. A. Hughes et T. P. Onak, *J. Amer. Chem. Soc.* **81**, 3166 (1959).
[9] H. Rapoport, R. J. Windgassen, N. A. Hughes et T. P. Onak, *J. Amer. Chem. Soc.* **82**, 4404 (1960).
[10] M.-M. Janot, R. Goutarel, A. Le Hir et F. Puisieux, *C. R. Acad. Sci., Paris* **248**, 108 (1959).
[11] F. Puisieux, R. Goutarel, M.-M. Janot et A. Le Hir, *C. R. Acad. Sci., Paris* **249**, 1369 (1959).
[12] F. Puisieux, A. Le Hir, R. Goutarel, M.-M. Janot et J. Le Men, *Ann. Pharm.* **17**, 626 (1959).
[13] F. Puisieux, R. Goutarel, M.-M. Janot, J. Le Men et A. Le Hir, *C. R. Acad. Sci., Paris* **250**, 1285 (1960).
[14] M.-M. Janot, J. Le Men, A. Le Hir, J. Levy et F. Puisieux, *C. R. Acad. Sci., Paris* **250**, 4383 (1960).
[15] F. Puisieux et A. Le Hir, *C. R. Acad. Sci., Paris* **252**, in press (1961); F. Puisieux, thése Doct. Sc. Paris (1960).
[16] A. Bertho, M. Koll et M. I. Ferosie, *Chem. Ber.* 2581 (1959).
[17] H. Bickel, H. Schmid et P. Karrer, *Helv. Chim. Acta* **38**, 649 (1955).
[17b] F. Percheron, R. Goutarel et C. Conreur, *Bull. Soc. Chim. Fr.* 1198 (1957).

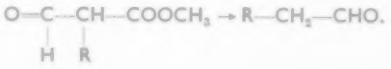
Cependant le spectre I.R. de la geissoschizine ne possède pas de bande vers 1720 cm^{-1}, mais il présente par contre à 1650 cm^{-1} une large bande qui permet d'envisager la présence d'un groupement ester β-aldéhydique.

Cette hypothèse est confirmée par le caractère facilement énolisable de la fonction aldéhyde (la geissoschizine est soluble dans les solutions aqueuses de soude) et par les faits suivants:

(a) La geissoschizine, traitée par la potasse aqueuses 2 N, à reflux, perd les éléments d'un carbonyle en donnant un acide $C_{19}H_{22}O_2N_2$, F = 213° don tle spectre U.V. est indolique



(b) La geissoschizine traitée par une solution aqueuse N d'acide chlorhydrique, à reflux conduit par décarboxylation à un aldéhyde VIII non cristallisable nommé cependant *geissoschizal* dont le spectre I.R. a une bande C=O à 1710 cm^{-1} et dont le spectre U.V. est indolique



(c) Le spectre U.V. de la geissoschizine résulte de la superposition de deux chromophores, celui de l'indole et celui du groupement ester β-énolique. Rapoport et ses collaborateurs ont pu reproduire le spectre U.V. de la geissoschizine (en milieu alcalin) par superposition du spectre d'un alcaloïde indolique et de celui de l'acétylacétate d'éthyle (dans la soude 0·1 N).[8]

Le squelette heterocyclique de la geissoschizine a été établi de la manière suivante par Rapoport et ses collaborateurs.[8] Ces auteurs réduisent le geissoschizal par la méthode de Wolff–Kishner. La deshydrogénation par le charbon palladié du dérivé desoxygéné obtenu, fournit *l'alstyrine*, II déjà préparée à partir de divers alcaloïdes dont la corynanthéine[18] et par synthèse.[19]

A la suite de quoi, ces auteurs proposent la formule plane III, très voisine de celle de la corynanthéine et de la corynanthéidine IV.

Nos travaux résumés dans le Tableau 1 confirment cette structure. Ils fixent le raccordement en position 15 de la partie oxygénée de la molécule et en 20 celle de la chaine éthylidène, en même temps que la stéréochimie.

En effet, il a été possible de préparer à partir de la corynanthéidine IV et de la geissoschizine III un dérivé commun, le corynantheidol V.

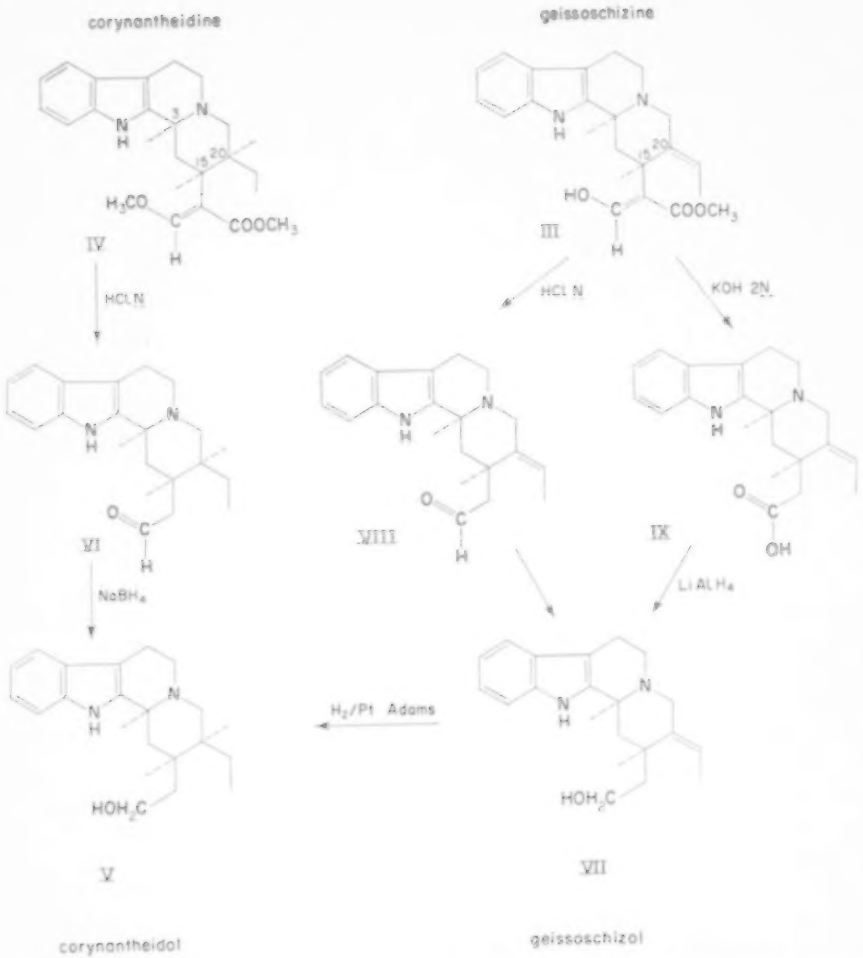
Le corynantheidal VI donne directement par le borohydrure de sodium, le corynantheidol déjà décrit.[20]

Le geissoschizol VII obtenu par réduction, soit du geissoschizal VIII par le borohydrure de sodium, soit de l'acide, $C_{19}H_{22}O_2N_2$ IX par $LiAlH_4$ est hydrogéné en présence de platine Adams, pour donner le corynanthéidol V identifié par son point de fusion et son spectre infra-rouge.

La configuration absolue de la geissoschizine III peut ainsi être déduite de celle de

[18] M.-M. Janot et R. Goutarel, *Bull. Soc. Chim. Fr.* 588 (1951).
[19] E. E. van Tamelen, P. E. Aldrich et J. J. Katz, *J. Amer. Chem. Soc.* **79**, 6426 (1957).
[20] C. Vamvacas, W. V. Philipsborn, E. Schlittler, H. Schmid et P. Karrer, *Helv. Chim. Acta* **40**, 1793 (1957).

TABLEAU I



la corynanthéidine, déjà établie[21] et confirmée par sa synthèse,[20] c'est-à-dire que cet alcaloïde vient encore enrichir le nombre des alcaloïdes qui ont l'hydrogène en position α sur le carbone 15 (selon la nomenclature des stéroïdes).

B. STRUCTURE DE L'APOGEISSOSCHIZINE

L'apogeissoschizine s'obtient soit au cours de l'hydrolyse de la geissospermine par l'acide chlorhydrique concentré, soit à partir de la geissoschizine par action de cet acide à froid ou par celle de l'acide polyphosphorique à 60°.[15]

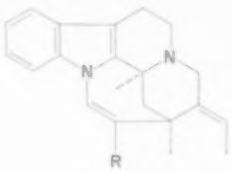
La base n'a pu être isolée à l'état cristallisé, mais elle donne un chlorhydrate qui cristallise dans l'ether-méthanol $C_{21}H_{22}O_2N_2$, HCl, (F = 145°). L'apogeissoschizine, qui ne diffère du point de vue analytique que par H_2O de la formule de la geissoschizine, a conservé le groupement carbométhoxyle et la chaine éthylidène. Par contre, elle ne renferme aucun hydrogène mobile et ne présente aucun caractère aldéhydique,

[21] M.-M. Janot, R. Goutarel, A. Le Hir, G. Tsatsas et V. Prelog, *Helv. Chim. Acta* **38**, 1073 (1955).

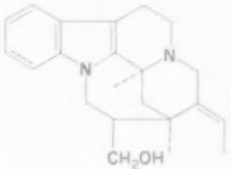
ce qui conduit à penser que la deshydratation se produit entre l'hydrogène actif du cycle indolique et l'hydroxyle de la fonction aldéhyde sous sa forme énolique pour donner X,[11] ce qui est en accord avec les spectres U.V. et I.R.[12] et confirmé par Rapoport et ses collaborateurs[9] qui ont fait la synthèse de produits possédant le même chromophore.

L'apogeissoschizine, par hydrolyse alcaline donne *l'acide apogeissoschizique* XI $C_{20}H_{20}O_2N_2$, (F = 176°). La réduction de la fonction ester par $LiAlH_4$ conduit à l'alcool primaire: *apogeissoschizol* XII $C_{20}H_{22}ON_2$, (F = 245°), $(\alpha)_D^{20}$ +64° (pyridine), lequel réduit par l'hydrogène en présence de platine Adams à la pression ordinaire et dans l'éthanol fournit le *dihydroapogeissoschizol* XIII $C_{20}H_{24}ON_2$, (F = 233°)[15] avec un rendement de seulement 30%. Le dihydroapogeissoschizol peut être acétylé par l'anhydride acétique, dans la pyridine. Le spectre I.R. de cet ester présente à 1720 cm^{-1} et 1220 cm^{-1} les bandes caractéristiques du groupement acétoxy.

Tous ces résultats confirment la structure X proposée pour l'apogeissoschizine.



X R = $COOCH_3$
XI R = COOH
XII R = CH_2OH



XIII

Il est intéressant de noter l'analogie de structure existant entre l'apogeissoschizine et la mavacurine, alcaloïde naturel isolé de différents *Strychnos*.[17]

Rapoport et ses collaborateurs ont réalisé le passage inverse de l'apogeissoschizine à la geissoschizine également par traitement par l'acide chlorhydrique concentré,[9] ce qui justifierait une étude particulière plus approfondie de la réaction car cette constatation présente un grand intérêt biogénétique: passage d'un alcaloïde du type corynanthéine à un alcaloïde du type mavacurine et inversement, or on sait quel rôle capital joue déjà la corynanthéine dans les hypothèses biogénétiques des alcaloïdes indoliques.

C. STRUCTURE DE LA GEISSOSCHIZOLINE

La geissoschizoline $C_{19}H_{26}ON_2$, (F = 126°), $(\alpha)_D^{21°}$ +32° (éthanol) possède: une chaîne $C(C_2H_5)$ (l'oxydation chromique donne de l'acide acétique et de l'acide propionique); deux atomes d'hydrogène mobiles correspondant à un NH et à un OH. L'un des atomes d'azote est basique et tertiaire, on obtient, en effet, un monoiodométhylate et un mono-chlorométhylate.

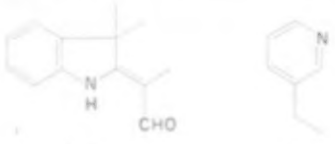
L'examen du spectre RNM élimine la présence d'un groupement $N—CH_3$, le second atome d'azote fait partie d'un hétérocycle indolinique comme le montre le spectre U.V. typique d'un dérivé indolinique 3–3' disubstitué. Elle donne un dérivé diacétylé dont le spectre I.R. présente les bandes caractéristiques du groupement acétoxy à 1710 cm^{-1} et 1220 cm^{-1} et celle d'une fonction amide disubstitué à 1635 cm^{-1}.

Le spectre U.V. (λ_{max}; (log ε): 252 mμ (4·17), 282 (3·66)) de ce composé est analogue à celui de la strychnine ce qui confirme la nature indolinique de l'hétérocycle

et d'autre part permet de déduire que l'atome d'azote dans la geissoschizoline est porteur d'un atome d'hydrogène et que l'atome d'oxygène de la geissoschizoline est alcoolique.

Cependant le spectre I.R. de la geissoschizoline ne présente qu'une large bande à 3350 cm^{-1} ce qui conduit à supposer que les deux groupements NH et OH révélés chimiquement, sont en chélation dans l'espace et ainsi voisins l'un de l'autre.

Ceci est confirmé par l'oxydation de la geissoschizoline, suivant la méthode d'Oppenauer en présence de butylate tertiaire de potassium, qui donne un composé cristallisé à fonction aldéhyde, de couleur jaune, (F = 212°), $(\alpha)_D^{21}$ −897° (éthanol) dont le spectre I.R. présente une large bande à 1560 cm^{-1}, et dont le spectre U.V. est identique à celui décrit par Karrer et ses collaborateurs[22] pour la fluorocurarine qui comporte le chromophore XIV.



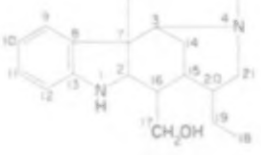
XIV XV

Ethyl−3 pyridine

Le pouvoir rotatoire remarquable est aussi comparable à celui des alcaloïdes α-méthylène-indolinique.

La formation de cet aldéhyde montre que la fonction alcool est primaire et autorise à situer cette fonction dans la position correspondante par rapport à l'hétérocycle indolinique.

Si l'on rapproche tous les résultats précédents du fait que Bertho, Koll et Ferosie[16] ont obtenu de l'ethyl-3 pyridine XV par dégradation de la geissoschizoline sur la poudre de zinc, il parait légitime d'attribuer à cet alcaloïde la structure de travail XVI[12] qu'il faut maintenant démontrer.



XVI

Cette structure pentacyclique XVI est établie sans ambiguité par les relations qu'elle présente avec l'akuammicine, alcaloïde extrait d'une autre Apocynacée, le *Picralima nitida* Stapf, mais avant de les exposer, il convient de décrire encore deux dérivés importants issus de la geissoschizoline.

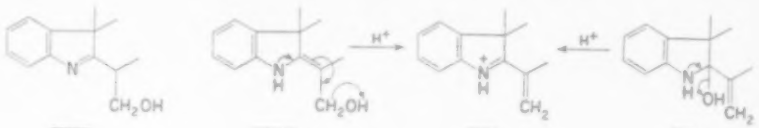
La geissoschizoline, oxydée par le permanganate de potassium en milieu acétonique, conduit à un dérivé insaturé à caractère d'amine tertiaire dont la formule $C_{19}H_{24}ON_2$ ne diffère que par H_2 de celle de la geissoschizoline, (F = 165°), $(\alpha)_D = -362°$ (pyridine) et qui possède encore la chaîne éthyle.

[22] K. Bernauer, F. Berlage, W. V. Philipsborn, H. Schmid et P. Karrer, *Helv. Chim. Acta* **41**, 2293 (1958).

Le spectre I.R. comporte une bande d'insaturation à 1560 cm^{-1} caractéristique selon Karrer[23] des alcaloïdes indoléniniques.

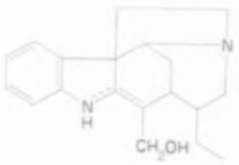
La formule partielle XVII interprète les faits, mais le pouvoir rotatoire élevé et négatif et l'obtention d'un monoiodométhylate conduisent à la formule XVIII.

Quant au spectre U.V. il correspond en milieu neutre à la sommation des spectres dûs aux chromophores XVII et XVIII, et en milieu acide N il y a déplacement vers les grandes longueurs d'ondes ce qui implique l'apparition d'un troisième chromophore du type XIX qui représente le cation commun à la forme alcool allylique XVIII et à la forme carbinolamine XX qui en dérive par transposition allylique.



XVII XVIII XIX XX

Deux positions sont donc à envisager pour la double liaison ce que représente la formule XXI attribuable au produit d'oxydation permanganique.



XXI

Cette délocalisation de la double liaison explique qu'aucune des réactions effectuées avec ce dérivé ne se présente comme univoque.

Un deuxième dérivé important de la geissoschizoline est celui qui résulte de la tosylation.

La geissoschizoline réagit avec le chlorure de tosyle, dans la pyridine, pour donner un tosylate amorphe qui, traité par la soude alcoolique N à reflux, ou par $LiAlH_4$ conduit à *l'anhydrogeissoschizoline*, corps non oxygéné, $C_{19}H_{24}N_2$; ($F = 128°$); $(\alpha)_D^{20°} +48°$ (éthanol).

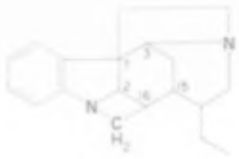
Cette base qui ne diffère de la geissoschizoline que par la perte de H_2O n'est pas hydrogénable catalytiquement par le platine Adams dans les conditions habituelles, elle ne comporte qu'un $C—CH_3$, pas d'hydrogène actif et n'est plus acétylable. Tout ceci peut s'interpréter par une deshydratation réalisée entre l'hydrogène actif de l'azote indolinique et la fonction alcool primaire (tosylée) et correspond à la formule XXII caractérisée par un cycle azoté à quatre éléments et par l'existence de 2 atomes d'azote tertiaire confirmés par l'obtention d'un dipicrate $C_{19}H_{24}N_2$, $2C_6H_3N_3O_7$; ($F = 230°$); $(\alpha)_D^{21°} +41°$ (pyridine).

Le spectre I.R. ne comporte ni bande OH, ni bande NH, mais bien la bande dihydroindole à 1580 cm^{-1}; le spectre U.V. est celui de la geissoschizoline décalé légèrement vers les petites longueurs d'ondes: [λ_{max}(log ε) 240 mμ, (3·75); 285 mμ (3·46)].

[23] K. Bernauer, W. Arnold, C. Weissmann, H. Schmid et P. Karrer, *Helv. Chim. Acta* **43**, 717 (1960).

Stéréochimie et configuration absolue

L'examen des modèles moléculaires montre d'une part que la formation d'anhydrogeissoschizoline n'est possible que si les atomes d'hydrogène portés par les carbone 2 et 16* de la geissoschizoline sont *cis* entre eux, et que d'autre part elle est facilitée s'ils sont *trans* par rapport à l'atome d'hydrogène porté par le carbone-15.



XXII

De plus la configuration des atomes de carbone-3 et -7 est nécessairement fixée par celle du carbone-15.

On peut donc déduire de l'anhydrogeissoschizoline la configuration relative la plus probable de la geissoschizoline.

La configuration absolue va être déterminée par les relations qui existent entre la geissoschizoline et l'akuammicine XXIII et l'aldéhyde de Wieland–Gümlich (Tableau 2) dont la structure et la stéréochimie sont parfaitement démontrées.[22,24–27]

L'akuammicine répond à la formule XXIII proposée par Aghoramurthy et Robinson en 1957,[28] puis confirmée presque simultanément dans trois laboratoires différents: à Zurich par Bernauer, Arnold, Weissmann, Schmid et Karrer[23], à Manchester par Smith et Wrobel[29] et à Paris par trois d'entre nous (Lévy, Le Men et Janot[30]).

Traitée par le zinc et l'acide sulfurique, l'akuammicine XXIII (Tableau 2) fournit, comme produit principal, la dihydro-2-16 akuammicine XXIV dont la réduction par $LiAlH_4$ de la fonction ester en alcool XXV, suivie de l'hydrogénation de la double liaison ethylidène 19–20, conduit à la geissoschizoline XXVI.[14]

La saponification de la dihydro-2-16 akuammicine XXIV fournit l'acide XXVII lequel réduit par $LiAlH_4$ se transforme en alcool XXVIII, identique à l'alcool obtenu par Karrer, Schmid et leurs collaborateurs à partir de la strychnine *via* l'aldéhyde de Wieland–Gümlich[22].

La stéréochimie de l'alcool XXVIII qui est parfaitement démontrée, permet de fixer celle de la geissoschizoline.

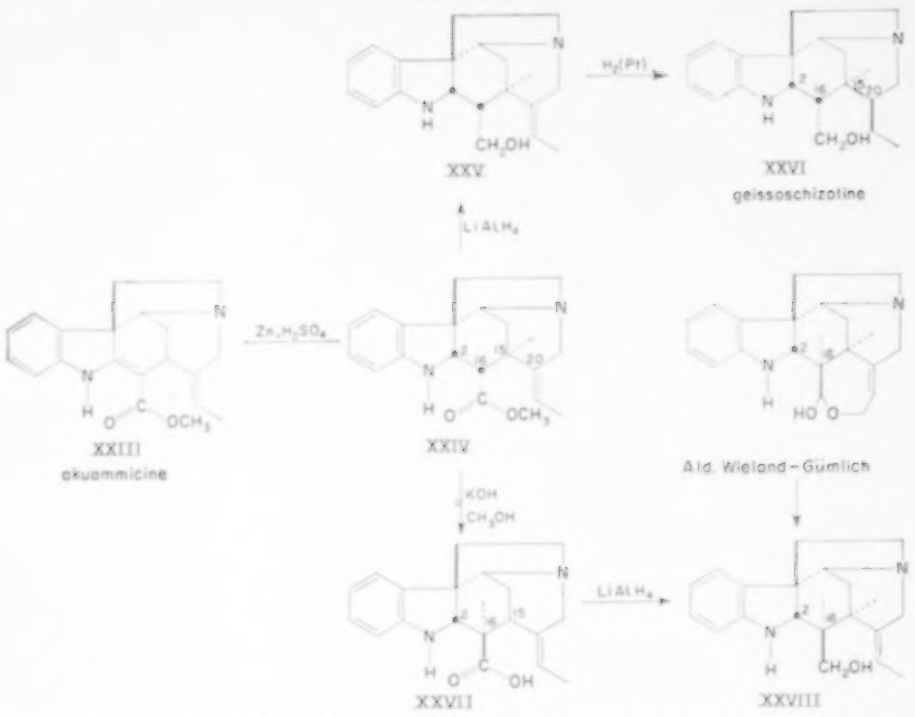
En effet, la configuration relative de la geissoschizoline vient d'être définie et la seule prise en considération de l'un des carbones homologues de ces deux alcaloïdes, C-15 par exemple, permet de déduire la configuration absolue XXVI de la geissoschizoline.

L'obtention à partir de la dihydro-2-16 akuammicine de la geissoschizoline (qui

* La nomenclature utilisée dûe à Mr. J. Le Men fera l'objet d'une prochaine note.

[22] H. Wieland et W. Gumlich, *Ann. Chem.* **494**, 191 (1932).
[23] H. Wieland et P. Kaziro, *Ann. Chem.* **606**, 60 (1933).
[24] F. A. L. Anet et R. Robinson, *Chem. & Ind.* 2253 (1953).
[25] A. F. Peerdeman, *Acta Cryst.* **9**, 824 (1956).
[26] K. Aghoramurthy et R. Robinson, *Tetrahedron* **1**, 172 (1957).
[27] G. F. Smith et J. T. Wrobel, *J. Chem. Soc.* 793 (1960).
[28] J. Levy, J. Le Men, M.-M. Janot, *Bull. Soc. Chim. Fr.* 979 (1960).

TABLEAU 2



est *cis* en 2–16) et celle de l'alcool XXVIII (qui est *trans* en 2–16) s'expliquent par l'épimérisation du carbone-16 au cours de la saponification.

Seule la configuration du carbone-20 n'est pas encore bien fixée.

Si l'on admet que lors de l'hydrogénation de la chaîne éthylidène de l'alcool XXV, le catalyseur doit s'approcher par le côté le moins encombré de la molécule, on peut attribuer à l'atome d'hydrogène en 20 la position α.

Une autre relation a pu être établie entre l'akuammicine et la geissoschizoline (Tableau 3).

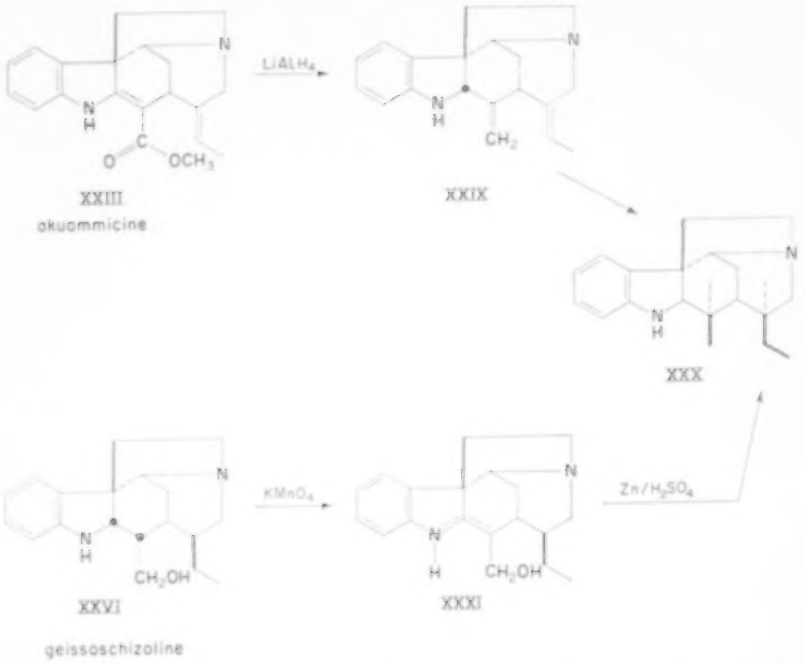
L'akuammicine XXIII réduite directement par $LiAlH_4$ conduit à un composé desoxygéné XXIX, $C_{19}H_{22}N_2$, (F = 196–197°), $(\alpha)_D$ −105° (alcool à 96°) porteur d'un exo-méthylène et dont l'hydrogénation catalytique fournit le composé XXX $C_{19}H_{26}N_2$, (F = 182°), $(\alpha)_D$ +30° (éthanol).

Le produit XXXI, décrit précédemment (XXI), de l'oxydation permanganique de la geissoschizoline, hydrogéné au moyen du zinc et de l'acide sulfurique conduit à un mélange de deux composés: l'un est la geissoschizoline, l'autre est identique au dérivé XXX issu de l'akuammicine.

Pour la même raison d'encombrement stérique que celle invoquée lors de l'hydrogénation catalytique du composé XXV, on peut attribuer aux atomes d'hydrogène du composé XXX, en position 16 et 20, l'orientation α.

L'hydrogénation catalytique en présence de platine Adams du produit XXXI d'oxydation permanganique de la geissoschizoline conduit à deux alcools isomères; l'un est la geissoschizoline elle-même XXVI, l'autre XXXII F = 85° est nécessairement

TABLEAU 3



XXIII
akuammicine

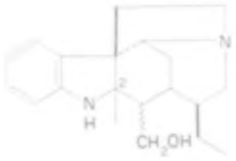
XXIX

XXX

XXVI
geissoschizoline

XXXI

20 α comme la geissoschizoline, mais il reste à déterminer la stéréochimie des carbones-2 et -16.



XXXII

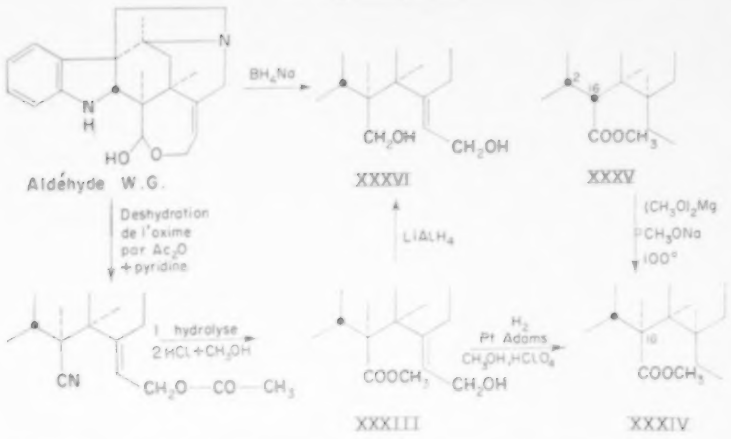
Cet alcool XXXII n'étant identique ni à la geissoschizoline (2β, 16β) ni au dérivé dihydrogéné en 19–20 (F = 218°) de l'alcool XXVIII issu de l'aldéhyde de Wieland–Gümlich* (2β, 16α) possède alors un hydrogène en 2 en orientation α.

Les conclusions précédentes sont confirmées par des travaux récents de G. F. Smith et ses collaborateurs.*

Ces auteurs ont préparé à partir de l'aldéhyde de Wieland–Gümlich le composé XXXIII qui possède une configuration absolue bien établie puisqu'il donne le même diol XXXVI que cet aldéhyde traité par BH_4Na.

L'hydrogénation de XXXIII en présence de platine Adams (et d'acide perchlorique) fournit le dérivé XXXIV qui peut également être préparé par épimérisation au moyen de méthanolate de sodium et de méthanolate de magnesium, de la tetrahydroakuammicine XXXV résultant elle-même de l'hydrogénation catalytique de la chaîne éthylidène de la dihydroakuammicine.

* Communication de Dr. Smith lors d'une récente visite au laboratoire et qui doit être prochainement publiée.

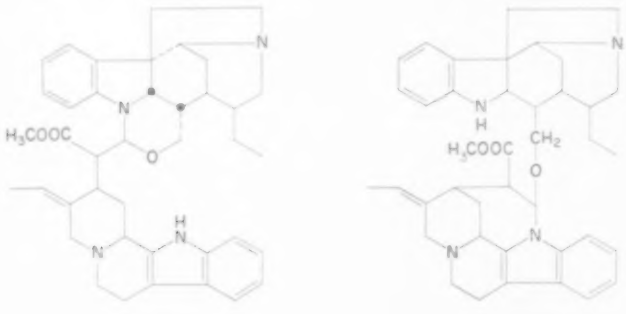


Ce qui montre bien la configuration de la tetrahydroakuammicine qui ne peut différer de son isomère XXXIV que par la configuration du carbone-16.

Ceci confirme enfin la configuration de la geissoschizoline qui est, comme nous l'avons vu, identique à celle de la tetrahydroakuammicine XXXV.

Geissospermine ou mode de jonction de la geissoschizine et de la geissoschizoline dans la geissospermine

En tenant compte de l'absence du chromophore H_3C OOC—C=C—O— de la geissoschizine et de la présence d'un seul atome d'hydrogène mobile dans la geissospermine, deux formules possibles furent envisagées pour cet alcaloïde: I et XXXVII. Mais la formule XXXVII n'explique pas pourquoi la geissospermine n'est pas acétylable alors que la geissoschizoline l'est, pas plus que l'obtention d'un seul produit sous l'action de l'hydrure d'aluminium–lithium.[10]



I XXXVII

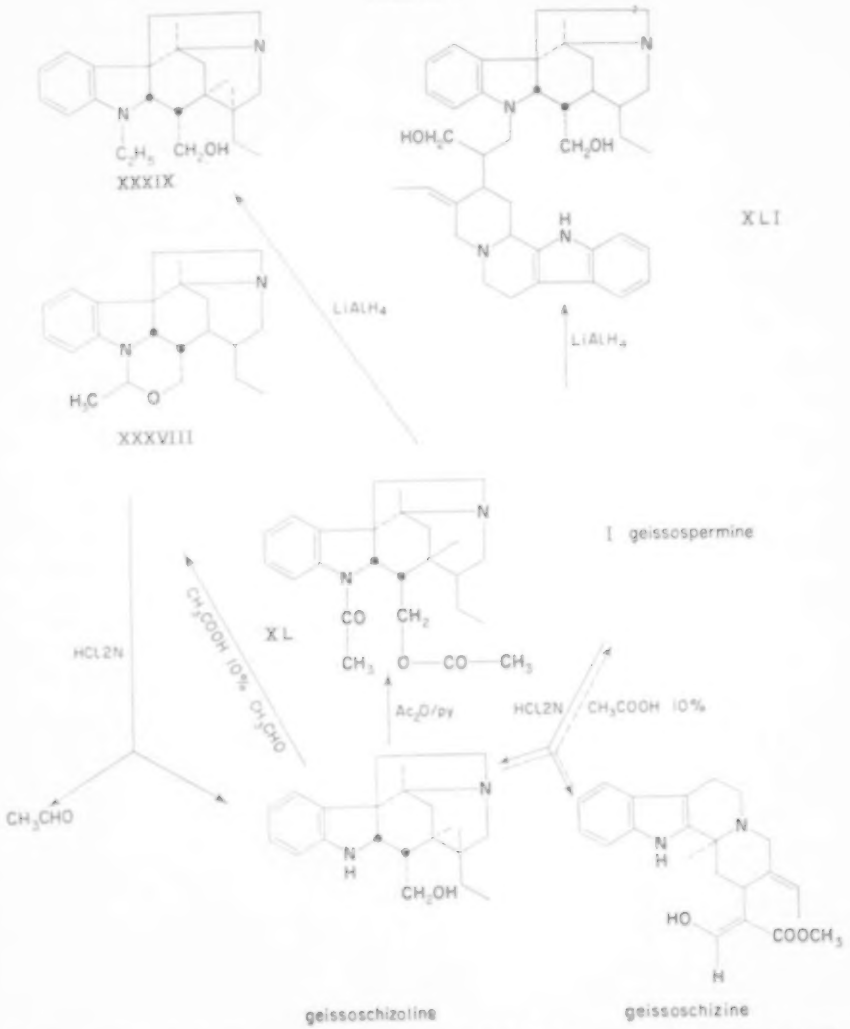
Par contre, la présence d'un cycle tetrahydro-métoxazine comme dans la formule I a été confirmée par l'étude de la condensation de la geissoschizoline avec un aldéhyde moins complexe que la geissoschizine, l'acetaldehyde (Tableau 4).[15]

En solution acétique à 10%, la geissoschizoline donne avec l'acetaldehyde la *méthylcarbogeissoschizoline* qui cristallise sous forme d'iodomethylate (F = 245°),

$(\alpha)_D^{20}$ +3° (méthanol). La base est hydrolysée par l'acide chlorhydrique 2 N pour redonner la geissoschizoline et l'acetaldehyde.

Sa structure est démontrée de la façon suivante: la methylcarbogeissoschizoline XXXVIII est réduite par $LiAlH_4$ en N-ethylgeissoschizoline XXXIX $C_{21}H_{30}ON_2$, (F = 189°), $(\alpha)_D^{20}$ −15° (méthanol) identifiée avec le produit de réduction par $LiAlH_4$ de la diacétylgeissoschizoline.

TABLEAU 4



La formation de la N-ethylgeissoschizoline XXXIX à partir de la méthylcarbogeissoschizoline XXXVIII explique celle du geissospermol XLI obtenu par réduction de la geissospermine par $LiAlH_4$. Dans cette réaction, il y a certainement réduction du groupement ester et ouverture du cycle tetrahydrométoxazine avec apparition de deux fonctions alcool primaire.

Le geissospermol (F = 180–183°), $(\alpha)_D^{20}$ −80° (éthanol) correspond donc à la formule $C_{39}H_{50}O_2N_4$[13] plutôt qu'à la formule $C_{39}H_{48}O_2N_4$ précédemment proposée.*[10]

La formule I peut donc être adoptée comme la plus probable pour la geissospermine. (Les atomes d'hydrogène en position β, c'est-à-dire au dessus de la molécule, sont représentés par un point noir-les liaisons α au dessous de la molécule sont en pointillé.)

* Il semble que Wiesner, Rideout et Manson[6] ont par $LiAlH_4$ ouvert le cycle tetrahydrometoxazine sans toucher au groupement ester tandis que Rapoport et ses collaborateurs à l'aide du sodium dans l'ammoniac liquide, ont réduit le groupement ester en alcool sans modifier le cycle tetrahydrometoxazine.

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STÉROÏDES AMINÉS NATURELS DES APOCYNACÉES

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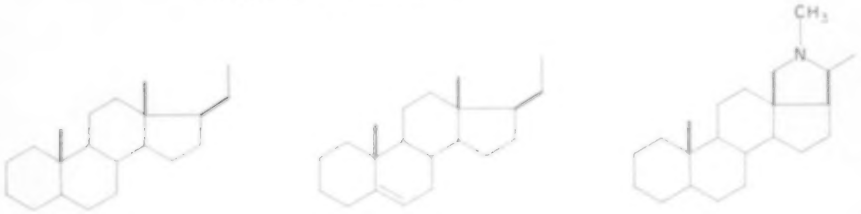
L'INTERET des alcaloïdes stéroïdes des Apocynacées s'est affirmé depuis quelques années, d'une part, parce qu'à la suite de l'établissement de leurs structures, les alcaloïdes des *Holarrhena* se sont montrés comme des matières premières intéréssantes dans la synthèse des stéroïdes substitués en position 18, et d'autre part, par la découverte dans de nombreuses Apocynacées, de bases stéroïdes simples, établissant toute une *filiation biogénétique* allant de la molécule du pregnane à la structure plus complexe des dérivés de la *conanine*.[1]

Ces résultats pérmettent de classer ces alcaloïdes† en 3 groupes:

—dérivés du (5α)-pregnane
—dérivés du pregna-5-ène et du pregna-8-ène
—dérivés de la conanine.



(5α) - pregnane pregna - 5 - ène conanine

Les travaux relatifs aux dérivés de la conanine, et en particulier, aux alcaloïdes du groupe de la conessine ont fait l'objet d'un article de Jeger et Prelog[2]. Le présent exposé ne traitera que des stéroïdes aminés récemment découverts dans les Apocynacées, recherches dont une grande part est dûe aux travaux du Laboratoire de Pharmacie Galénique de la Faculté de Pharmacie de Paris que dirige le Professeur M-M. Janot.

Derivés du (5α) *pregnane: alcaloïdes des* Funtumia *et des* Malouetia

Le genre *Funtumia* Stapf était autrefois inclus, avec le nouveau genre *Kibatalia* G. Don, dans l'ancien genre *Kickxia* Bl. Ces deux nouveaux genres font partie de la sous-tribu des *Kibatalinées* et de la sous-famille des *Echitoïdées*.

Les *Funtumia* sont des arbres de l'Afrique tropicale, dont on connait 3 éspèces: *F. latifolia* Stapf, *F. africana* (Benth) Stapf et *F. elastica* (Preuss) Stapf.

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† Doit-on conserver le terme d'alcaloïdes pour des bases stéroïdes aussi simples que la funtumine? Les alcaloïdes étant des produits naturels azotés, basiques, et présentant vis-à-vis de certains réactifs généraux, des réactions particulières, ainsi que des propriétés pharmacodynamiques appréciables, nous employons, indifféremment les éxpréssions de stéroïde aminé ou d'alcaloïde uniquement pour éviter des redites.

[1] R. D. Haworth et M. Michaël, *J. Chem. Soc.* 4973 (1957).
[2] O. Jeger et V. Prelog, *The Alkaloids* (Edited by R. H. F. Manske) Vol. VII. Academic Press, New York (1960).

Le *Funtumia elastica* est un arbre des grandes forêts de l'Afrique Equatoriale et Occidentale, connu depuis longtemps comme fournissant un excellent caoutchouc, le *caoutchouc de l'Ireh*. Nos recherches faites sur de petites quantités de drogue, originaire du Congo ex-Belge, ont montré des teneurs en alcaloïdes totaux de 0·6% dans les écorces, 0·4% dans les racines et de 1·8% dans les feuilles. De ces dérnières, a été retiré un alcaloïde cristallisé, dénommé *iréhine*, dont l'étude chimique est en cours.[3]

Le *Funtumia latifolia* est un arbre de l'Afrique Occidentale, très répandu dans toute la région des grandes forêts, en Guinée, Libéria, Côte d'Ivoire, Ghana etc. On ne trouve aucune indication d'une étude chimique de cette éspèce, jusqu'à la découverte, en 1958, de la *funtumine* et de la *funtumidine*.[4] Les feuilles de *Funtumia latifolia* sont très riches en alcaloïdes totaux, environ 3·5%, dont 1·6% de funtumine et 0·4% de funtumidine. Les écorces sont moins riches—de 0·45 à 0·8%—et l'on en a retiré, en petites quantités,[3] deux autres alcaloïdes: *latifoline* (0·02%) et *funtumafrine* C (0·02%). Quant aux racines, la teneur en alcaloïdes totaux est de l'ordre de 0·15%.

La structure de la *Funtumine* I, peut être établie facilement par deux réactions simples:

—d'une part la désamination oxydative de la funtumine, selon la méthode de Ruschig[5], conduit au dérivé connu: le 3,20 dioxo(5α)pregnane II. La même désamination peut être faite par une nouvelle méthode d'oxydation par le chlorite de sodium, catalysée par le tétroxyde d'osmium, et mise au point par Pappo[6].

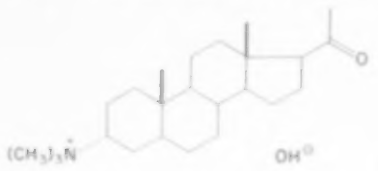
—d'autre part, la funtumine, méthylée selon la méthode d'Eschweiler–Clarke[7] à l'acide formique/formaldéhyde, et réduite ensuite selon Wolff–Kischner[8] conduit au 3α-diméthylamino(5α)pregnane III, identique au dérivé préparé par Haworth[9] au cours de ses recherches sur la structure de la conessine. La funtumine est donc le 3α-amino 20-oxo(5α)pregnane I. La présence d'une fonction amine primaire a été mise en évidence par les reactions classiques de cette fonction: formation d'acétamide, dérivé N-benzylidène etc. et aussi grâce à la spectrographie infra-rouge, qui permet de caractériser la présence d'une bande NH_3^+ à 2031 cm^{-1} dans le chlorhydrate de funtumine. D'après Khuong-Huu[3] l'examen des spectres I.R. des chlorhydrates d'amines stéroïdes, permet de distinguer les amines primaires, secondaires et tértiaires

II I III

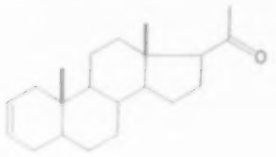
grâce aux vibrations correspondant aux groupes NH_3^+, NH_2^+ et NH^+. Ces résultats sont fidèles et caractéristiques, particulièrement pour les dérivés aminés du 5α-pregnane. Le spectre I.R. de la funtumine présente, d'autre part une forte bande carbonyle à 1695 cm^{-1}. La configuration 3α de la fonction amine primaire de la

[3] Khuong-Huu Qui, *Alcaloïdes Stéroïdes des Funtumia*. Thèse Dr Sc. Paris (1960).
[4] M.-M. Janot, Q. Khuong-Huu et R. Goutarel, *C.R. Acad. Sci., Paris* **246**, 3076 (1958); *Ibid.* **248**, 982 (1959).
[5] H. Ruschig, W. Fritsch, J. Schmidt-Thomé et W. Haede, *Chem. Ber.* **88**, 883 (1955).
[6] R. Pappo, U.S. Pat. 2.919.285 (1959).
[7] W. Eschweiller, *Chem. Ber.* **38**, 880 (1905); H. T. Clarke, H. B. Gillespie et S. Z. Weisshaus, *J. Amer. Chem. Soc.* **55**, 4571 (1933).
[8] M.-M. Janot, Q. Khuong-Huu, X. Lusinchi et R. Goutarel, *Bull. Soc. Chim. Fr.* 1669 (1960).
[9] H. Favre, R. D. Haworth, J. McKenna, R. G. Powell et R. G. Whitfield, *J. Chem. Soc.* 1115 (1953).

funtumine est confirmée par la dégradation, selon la méthode d'Hofmann, de l'hydroxyde de triméthylfuntuminium IV, conduisant au Δ^2, 20-oxo(5α)prégnène V. Ce dérivé étant connu, son obtention confirme la position en 20 de la fonction cétone.



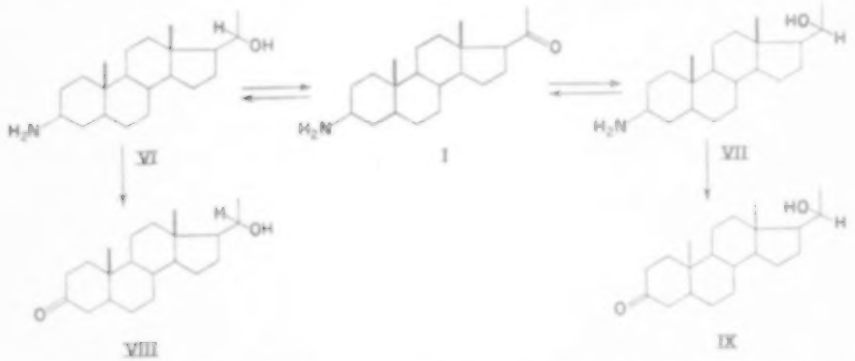
IV



V

Les travaux de Haworth[10] ont montré que dans la série du cholestane et du 5α-pregnane (série A/B trans) la dégradation, selon Hofmann, des ammoniums quaternaires 3α conduisait facilement au dérivé insaturé, alors que celle réalisée sur les composés 3β donnait, en majeure partie, le dérivé 3β-diméthylamino. L'obtention d'une oléfine, avec élimination de triméthylamine, à partir de l'hydroxyde de funtuminium, est en accord avec la conformation axiale du groupement 3α-amino de la funtumine.

La *funtumidine* VI, possède une fonction amine primaire et une fonction alcool secondaire. L'oxydation chromique de la funtumidine conduit à la funtumine I. Il suffit donc de déterminer la configuration de la fonction OH en 20 pour établir la



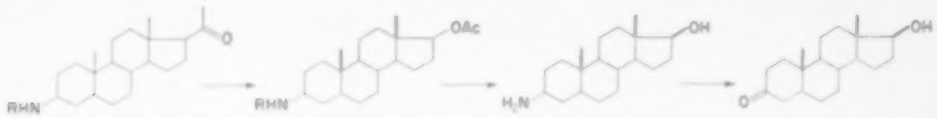
VI I VII

VIII IX

structure de la funtumidine. La réduction de la funtumine par le borohydrure de potassium, conduit à un isomère de la funtumidine, *l'isofuntumidine* VII. On sait qu'une telle réduction oriente, dans les stéroïdes, la fonction hydroxyle en 20β, d'une façon prépondérante. D'autre part, la réduction de la funtumine, par le sodium/éthanol, a donné la funtumidine. Cette dérnière réduction, stéréospécifique, oriente le groupe OH en 20α, en majeure partie. La funtumidine VI est le 3α-amino 20α-hydroxy(5α)pregnane et l'isofuntumidine VII, le 3α-amino 20β-hydroxy(5α)pregnane. Ces strutures sont confirmées par l'obtention, par application de la méthode de Ruschig, des 2 cétones-alcools connus: le 3-oxo 20α-hydroxy(5α)pregnane VIII et le 3-oxo 20β-hydroxy(5α)pregnane IX. Les rendements appréciables, en alcaloïdes, des feuilles de *Funtumia latifolia* amènent à les considérer comme des matières premières dans la synthèse de stéroïdes simples. Un certain nombre de dérivés du 5α-pregnane

[10] R. D. Haworth, J. McKenna et R. G. Powell, *J. Chem. Soc.* 1110 (1953).

ont été ainsi préparés, à partir de la funtumine et de la funtumidine,[3,8] ainsi que des dérivés du 5α-androstane à partir de la funtumine.[3,11] Les dérivés acétylé Xa ou trifluoroacétylé Xb de la funtumine, traités par les peracides, conduisent aux dérivés corréspondants XIa et XIb du 3α-amino-17β-hydroxy(5α)androstane XII. Aprés saponification et désamination, selon Ruschig, on obtient l'androstanolone XIII.



Xa ,R=Ac; Xb,R=CF_3CO XIa et XIb XII XIII

Le *Funtumia africana* est un arbre plus rare que les précédents et que l'on rencontre surtout en Afrique Equatoriale, plus particulièrement au Congo.

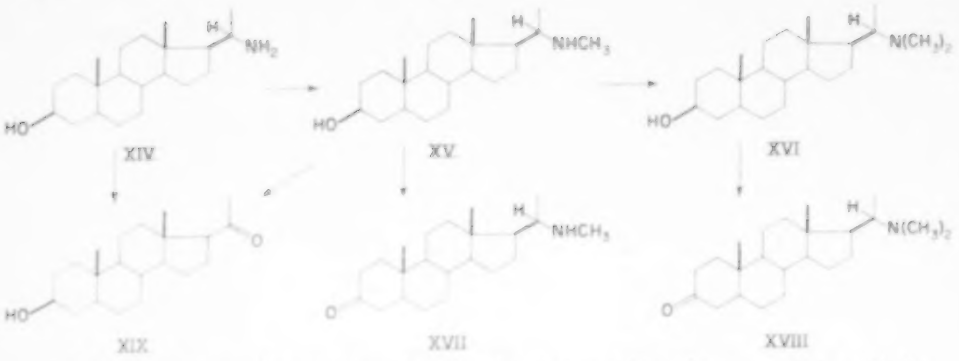
On trouve en 1931 une étude faite par Wattiez et Sternon[12] sur les graines de *Kickxia africana* (syn. *F. africana*). Ces auteurs en ont retiré un alcaloïde dont le sulfate fond à 187°. Nous avons caractérisé la présence d'alcaloïdes dans les écorces (1·2‰), les racines (0·4‰) et les feuilles (1·7‰) de *Funtumia africana*. La teneur en alcaloïdes totaux est moins grande que dans les feuilles de *F. latifolia*, mais, étant donnée la découverte de la funtumine et de la funtumidine, nos premiers travaux ont porté sur les feuilles de *Funtumia africana*. Les alcaloïdes ont été séparés en *bases A*, donnant des sulfates solubles dans l'eau et en *bases B* dont les sulfates sont insolubles. Seules les bases A, plus facilement purifiables ont été étudiées jusqu'ici, et les différents alcaloïdes séparés par chromatographies successives.

Ces chromatographies pérmettent de séparer, d'abord des amines à fonction cétone, puis des amino-alcool. Les amino-cétones ont été nommées *funtumafrines:* ce sont la *funtumafrine B* (amine secondaire) et la *funtumafrine C* (amine tertiaire). Les amino-alcools sont nommés *funtuphyllamines:* ce sont la *funtuphyllamine A* (amine primaire), la *funtuphyllamine B* (amine secondaire), la *funtuphyllamine C* (amine tértiaire).[3,13]

La *funtuphyllamine A*, XIV, est une amine primaire possédant une fonction alcool secondaire. La désamination de cette base, par la méthode de Ruschig, conduit au 3β hydroxy-20 oxo(5α)pregnane XIX. Il suffit de détérminer la configuration de la fonction amine en 20 pour connaître la structure de la funtuphyllamine A. Disons, tout de suite que cet alcaloïde est le 3β hydroxy-20α amino(5α)pregnane, la configuration 20α (configuration des dérivés naturels) ayant été détérminée par synthèse partielle et par les opérations suivantes.

La *funtuphyllamine B* XV est une amine secondaire, possédant une fonction alcool secondaire. Sa désamination conduit, elle- aussi, au 3β hydroxy-20 oxo(5α)pregnane XIX. Nous avons ici une preuve de la configuration 20α de la funtuphyllamine B, puisque ce dérivé a été préparé par Jeger[14] comme intérmédiaire de la synthèse de la conanine. Cet alcaloïde est le 3β hydroxy-20α methylamino(5α)pregnane. Il peut être obtenu à partir de la funtuphyllamine A, par réduction au moyen de l'hydrure d'aluminium–lithium, du dérivé diformylé (amide-ester) de la base amine primaire. Ceci confirme la configuration 20α de la funtuphyllamine A.

[11] M.-M. Janot, Q. Khuong-Huu et R. Goutarel, *Bull. Soc. Chim. Fr.* 1640 (1960).
[12] N. Wattiez et F. Sternon, *J. Pharm. Belg.* **13**, 139 (1931).
[13] M.-M. Janot, Q. Khuong-Huu et R. Goutarel, *C.R. Acad. Sci., Paris* **250**, 2445 (1960).
[14] P. Buschacher, J. Kalvoda, D. Arigoni et O. Jeger, *J. Amer. Chem. Soc.* **80**, 2905 (1958).



XIV XV XVI

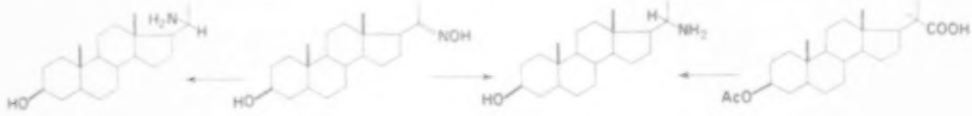
XIX XVII XVIII

La *funtuphyllamine C* est une amine tértiaire, qui peut être obtenue, soit à partir de la funtuphyllamine A, soit à partir de la funtuphyllamine B par méthylation selon la méthode d'Eschweiler à l'acide formique/formaldéhyde. C'est le 3β hydroxy 20α diméthylamino(5α)pregnane, XVI. Ce dérivé, ainsi que son ester acétique, avait été antérieurement préparé par Sorm[15] et l'acétylfuntuphyllamine C est identique au 3β acétoxy-20α diméthylamino(5α)pregnane.

La *funtumafrine B*, XVII, peut être préparée par oxydation chromique de la funtphyllamine B. C'est donc le 3 oxo-20α méthylamino(5α)pregnane.

La *funtumafrine C*, XVIII, dérive de la funtuphyllamine C, par oxydation chromique. Elle est identique au 3 oxo-20α diméthylamino(5α)pregnane déjà décrit par Sorm[15].

Tous ces dérivés naturels ont pu être préparés, par synthèse stéréospécifique, à partir du 3β hydroxy-20 oxo(5α)pregnane. Les travaux de Sorm[15] avaient montré que la réduction du 3β hydroxy-20-cétoximo(5α)pregnane, XX, par le sodium/éthanol, conduisait, d'une façon préférentielle, à l'amine 20β; XXI. Sorm avait préparé le dérivé 20α par application de la réaction de Curtius à l'acide acétoxy-bisnor-*allo*-cholanique XXII. On sait que la réaction de Curtius se fait sans inversion de la



XXI XX XIV XXII

configuration et le dérivé obtenu a bien la configuration 20α. Cette amine primaire n'avait cependant pas été isolée, mais méthylée directement pour donner le 3β hydroxy-20α diméthylamino(5α)pregnane, XVI, qui est d'ailleurs identique à la funtuphyllamine C.

Nous avons montré que la réduction catalytique de l'oxime XX, conduit, par hydrogénation en présence de platine Adams et en solution acétique, à un mélange des deux dérivés 20α et 20β contenant environ 70% de la forme 20α. De cette manière, nous avons préparé la funtuphyllamine A, qui a été monométhylée en funtuphyllamine B et diméthylée en funtuphyllamine C. L'oxydation de ces deux dérnières, par l'acide chromique ou par la méthode d'Oppenauer, a donné les deux funtumafrines B et C.

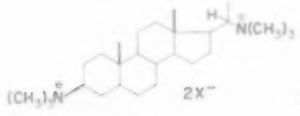
[15] V. Cerny, L. Labler et F. Sorm, *Coll. Czech. Chem. Comm.* **22**, 76 (1957).

Le genre *Malouetia* A. DC. fait partie de la sous-tribu des *Malouétinées* et de la sous-famille des *Echitoïdées*. Ce genre comprend 27 éspèces, dont 24 appartiennent á l'Amérique du Sud et 3 á l'Afrique Equatoriale.

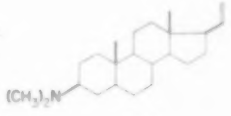
Le *guachamacha* est une drogue vénézuélienne dont l'origine a été rapportée au *Malouetia schomburgkii* M.-Arg.. D'apres Planchon[16], Schiffer en aurait isolé un alcaloïde impur la *guachamachine à* action curarisante. On trouvera dans Planchon[16] et dans une monographie de Bisset[17] sur les alcaloïdes des Apocynacées, l'historique du guachamacha et du genre *Malouetia*.

L'étude pharmacologique et chimique du guachamacha date du siècle dérnier et mérite d'être reprise. Bisset fait l'intéréssante suggestion, que la guachamachine pourrait être un alcaloïde bisindolique diquatérnaire du type des alcaloïdes en C_{40} retirés des Strychnos et étudiés par Karrer.[18] Les *Malouetia* feraient ainsi le pont entre les alcaloïdes curarisants des *Strychnées* et les alcaloïdes en C_{40} retirés de cértaines Apocynacées: *Voacanga*[19], *Geissospermum*[20] etc. C'est éffectivement à ce titre que ces plantes nous intéréssaient et nos travaux ont porté sur le *Malouetia bequaertiana* E. Woodson, originaire du Congo ex-Belge. Nous avons caractérisé la présence d'alcaloïdes dans les écorces, les racines et les feuilles de cette éspèce. Les alcaloïdes des écorces et des racines ont été séparés en bases faibles solubles dans les solvants organiques (ether, chlorure de méthylène) et bases fortes solubles dans l'eau. Les feuilles ne contiennent pas de bases fortes.[21]

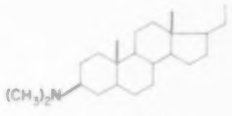
A notre grand étonnement, nous avons isolé, des bases faibles, deux alcaloïdes précédemment retirés de *Funtumia africana:* dans les écorces, la *funtuphyllamine B* et dans les feuilles, la *funtumafrine C*, à coté d'une base dont la structure n'a pas été établie, la *malouphylline*. Des bases fortes, dans les écorces et les racines, nous avons séparé sous forme de perchlorate, de picrate et de chlorure, une seule base que nous avons nommée *malouétine*. L'activité pharmacodynamique de la malouétine a été étudiée par Quevauviller et Lainé[22] et cette *activite curarisante* représente celle de la drogue. Signalons que Raffauf *et al.*[23] ont étudié récemment le *Malouetia arborea;* la présence de bases quatérnaires est signalée, mais celles-ci n'ont pas été isolées. La pharmacodynamie des bases faibles—qui ne sont pas curarisantes—a été ébauchée.



XXIII



XXIV



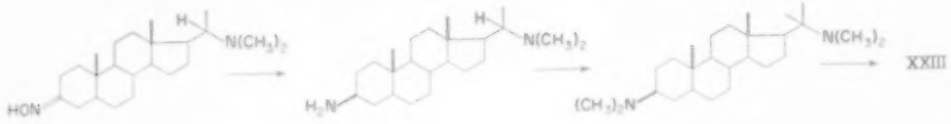
XXV

La *malouétine*, XXIII, est une base diquatérnaire dont le spectre U.V. est transparent, ce qui indique tout d'abord, qu'elle ne fait pas partie des curarisants isoquinoléiques ou indoliques. Cette base constitue une nouvelle classe de curarisant naturel et son étude chimique présente, de ce fait, un grand intérèt théorique et pratique. La

[16] L. Planchon, *Produits fournis à la Matière Médicale par la Famille des Apocynées*. Montpellier (1894).
[17] N. G. Bisset. *Ann. Bogoriensis* **3**, 105 (1958).
[18] E. Bächli, C. Vamvacas, H. Schmid et P. Karrer, *Helv. Chim. Acta* **40**, 1167 (1957).
[19] F. Percheron, *Contribution à l'étude des Voacanga*. Thèse Dr. Sc., Paris (1958).
[20] M.-M. Janot, *Tetrahedron* **14**, 113 (1961).
[21] M.-M. Janot, F. Lainé et R. Goutarel, *Ann. Pharm. Fr.* **18**, 673 (1960).
[22] A. Quevauviller et F. Lainé, *Ann. Pharm. Fr.* **18**, 678 (1960).
[23] R. F. Raffauf, E. Macko et O. Ribeiro, *J. Med. Pharm. Chem.* **2**, 239 (1960).

pyrolyse sous vide de la malouétine, conduit à un dérivé monobasique, la *malouétiméthine*, XXIV, possédant une double liaison. L'hydrogénation de la malouétiméthine conduit au 3β diméthylamino(5α)pregnane, XXV, identique au produit de synthèse décrit par Haworth.[9]

Ces résultats permettent de supposer que la malouétine est le 3β, 20α bis-triméthylammonium(5α)pregnane. En effet, nous savons que la dégradation selon la méthode d'Hofmann, des 3β triméthylammoniums, dans la série stéroïde A/B trans, conduit à l'amine tértiaire 3β. D'autre part, la formation de la double liaison de la malouétiméthine, avec élimination de triméthylamine, est le résultat d'une dégradation d'Hofmann classique. Le second groupe ammonium quatérnaire se trouve donc, soit en 20, soit en 21, mais plus vraisemblablement, dans un dérivé naturel, en 20α. Nous avons démontré cette structure, par synthèse de la malouétine à partir de la funtumafrine C. L'oxime de la funtumafrine C, XXVI, a été réduit par le sodium, dans l'éthanol bouillant. On sait que cette réduction oriente, préférentiellement, la fonction amine primaire en 3β, alors que la réduction catalytique conduit principalement au dérivé 3α 3. La diamine XXVII, ainsi obtenue, a été méthylée en 3β diméthylamino-20α diméthylamino(5α)pregnane XXVIII. Ce dernier, traité par l'iodure de méthyle, conduit au *diiodure de malouetinium*, XXIII, X = I. A partir de ce sel, nous avons



XXVI XXVII XXVIII

préparé le perchlorate, le chlorure et le picrate de malouétine. Tous ces sels sont identiques aux dérivés correspondants du produit naturel et le spectre I.R. du picrate synthétique est superposable à celui du picrate naturel.

Devant ce résultat, nous avons préparé les 3 isomères possibles de la malouétine: 3β —20β, 3α —20α et 3α —20β, dans l'intention de faire une étude pharmacodynamique complète de ces nouveaux curarisants.

Dérivés du prégna-5-ène: alcaloïdes des Holarrhena (*feuilles*) *et du* Paravallaris microphylla

La présence de dérivés simples du 5α pregnane dans les Apocynacées, nous a fait penser qu'il devait nécessairement exister les dérivés correspondants possédant une double liaison et appartenant à la série du pregna-5-ène. C'est, vraiment, en faisant cette hypothèse, et en nous basant sur la présence de stéroïdes aminés simples dans les feuilles de *Funtumia*, que nous avons été amenés à étudier les feuilles des *Holarrhena*, puisqu'il est connu que les écorces de ce genre contiennent des alcaloïdes du groupe du pregna-5-ène et, en particulier, l'*holarrhimine* XLV, précurseur éventuel de la *conessine* XLVI.

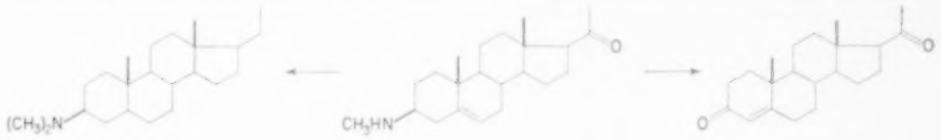
Le genre *Holarrhena* R. Br. fait partie de la sous-tribu des *Holarrhinées* et de la sous-famille des *Plumeroïdées*. Ce genre comprend 7 *à* 8 éspèces constituées par de petits arbres ou arbustes buissonants originaires de l'Afrique Tropicale, de l'Est asiatique et de Java. Il est divisé en 2 séctions: *Euholarrhena* A. DC. et *Alepis* A. DC. Les principales recherches faites auparavant, ont porté sur les écorces et les graines de trois éspèces principales: *Holarrhena antidysenterica* (Roxb.) Wall., *Holarrhena congolensis* Stapf et *Holarrhena floribunda* (G. Don) Dur et Schinz. L'éspèce *H. congolensis* est

considerée comme douteuse par Pichon[24] qui la range dans la séction *Alepis* et en fait un synonyme de *H. floribunda*.

Il est curieux de noter que les travaux précédents ont porté, presque uniquement, sur les écorces et les graines de ces éspèces. Ceci tient, sans doute, à ce que la drogue indienne, le *kurchi*, fourni par *H. antidysenterica*, est constituée par les écorces (écorces de conessie) et les graines (graines d'*Anderjow*). Seuls Dutta[25] a éffectué des dosages comparés d'alcaloïdes totaux dans les écorces de tronc, les écorces de racines et les feuilles de *H. antidysenterica* et, Paris et Schmit[26,27] ont dosé 0·06 à 0·35% d'alcaloïdes totaux dans les feuilles *d'H. floribunda*.

Nous avons tout d'abord, repris l'étude des alcaloïdes des feuilles de l'éspèce africaine *Holarrhena floribunda*, dont le synonyme le plus couramment utilisé est *H. africana* A. DC. Les rendements en alcaloïdes totaux que nous avons obtenus (1·66 à 1·9%) sont plus élevés que ceux signalés par Paris. Nous n'avons pas trouvé de conessine dans ces feuilles, mais trois alcaloïdes stéroïdes dénommés: *holaphylline*, *holaphyllamine* et *holamine*.[28,29]

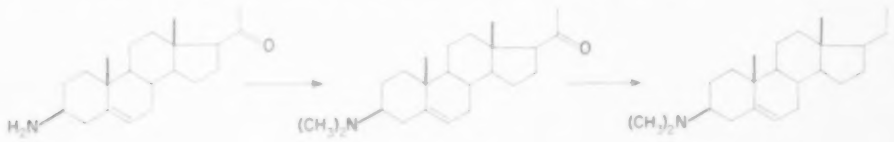
L'*holaphylline* possède une fonction cétone, une fonction amine secondaire ($NHCH_3$) et une double liaison hydrogénable, en présence de palladium et en solution acétique.



XXX XXIX XXXI

Après méthylation, hydrogénation et réduction de la fonction cétone par Wolff-Kischner, on obtient un dérivé connu, le 3β diméthylamino(5α)pregnane, XXX. D'autre part, la désamination de l'holaphylline, selon Ruschig, conduit à la progestérone XXXI. La position de la double liaison est détérminée par identification de la dihydrodesoxo-methylholaphylline, XXXII, au 3β diméthylamino-pregna-5-ène antérieurement préparé par Haworth.[9] Cette position est confirmée par la méthode des différences de rotation moléculaire, entre les dérivés insaturés préparés à partir de l'holaphylline et les dérivés saturés correspondants. La structure de l'holaphylline, XXIX, est celle du 3β méthylamino-20 oxo-pregna-5-ène.

L'*holaphyllamine* XXXIII, conduit par méthylation à un dérivé identique à la méthylholaphylline XXXIV, dont la réduction, selon Wolff-Kischner, a donné le 3β diméthylamino-pregna-5-ène XXXII. L'holaphyllamine est l'amine primaire correspondant à l'holaphylline. C'est le 3β amino-20 oxo-pregna-5-ène.



XXXIII XXXIV XXXII

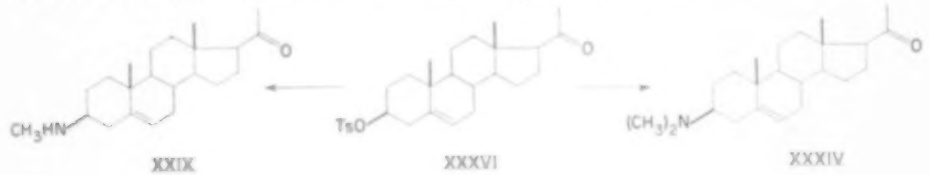
[24] M. Pichon, *Mém. Mus. Hist. Nat., Paris* (*sèr. B, Bot*) **1**, 145 (1950).
[25] A. T. Dutta, B. K. Ghosh et J. C. Gupta, *Ind. J. Méd. Res.* **38**, 467 (1950).
[26] R. Paris, *Bull. Soc. Pharm.* **49**, 33 (1942).
[27] A. Schmit, Thèse Fac. Pharm., Paris (1950).
[28] M.-M. Janot, A. Cavé et R. Goutarel, *Bull. Soc. Chim. Fr.* 896 (1959).
[29] M.-M. Janot, A. Cavé et R. Goutarel, *C.R. Acad. Sci., Paris* **251**, 559 (1960).

L'*holamine*, XXXV, est une amine primaire cétonique, dont l'hydrogénation catalytique (Pd/acide acétique) conduit à la funtumine, I. La désamination de cette base, par la méthode de Ruschig, a donné la progéstérone, XXXI. L'holamine corre-

I XXXV XXXI

spond à une *dehydrofuntumine*. La double liaison est située nécessairement en 4,5 ou en 5,6. Nous avons pensé que cette double liaison était située en 5,6 et proposé pour l'holamine, la structure du 3α amino-20 oxo-pregna-5-ène qui en fait l'épimère 3α de l'holaphyllamine. Cependant cértains résultats anormaux, dans les réactions faites à partir de l'holamine, permettent de douter de la position proposée pour la double liaison. En effet, il est connu[20] que les dérivés 3α substitués du pregna-5-ène, conduisent par hydrogénation catalytique à la série stéroïde A/B *cis*, ce qui n'est pas le cas de l'holamine conduisant à la funtumine. En l'absence de corps de référence, permettant de lever l'incertitude, la position de cette double liaison devra ètra détérminée par les méthodes d'oxydation utilisées dans le cas de la conessine.

Nous avons réalisé la synthèse de l'holaphylline et de la méthylholaphylline, en faisant réagir sur le "*tosylate*" de 3β hydroxy-20 oxo-pregna-5-ène, XXXVI, la méthylamine et la diméthylamine. Des réactions de ce type ont été étudiées par Julian et Magnani dans la série du cholesterol[21] et par Haworth[10] dans la série du pregna-5-ène. Il est connu que l'on obtient, par cette réaction, 3 dérivés: une amine 3α, une amine 3β et une amine 6β de la série 3,5 cyclostéroïde (*isosteroïdes*), XXXVIII.



XXIX XXXVI XXXIV

XXXVII XXXVIII

Le dérivé 3β méthylamino est bien identique à l'holaphylline XXIX, et le 3β diméthylamino à la méthylholaphylline XXXIV. Par contre les dérivés XXXVII et XXXVIII ne correspondent à aucun des dérivés de l'holamine.

Nous avons étudié deux échantillons d'*Holarrhena antidysenterica*, en provenance, l'un du Viet-Nam, l'autre des Indes. De l'échantillon Vietnamien nous avons caractérisé, dans les feuilles, une amine cétonique, dénommée *holadysine*, de formule

[20] J. R. Lewis et C. W. Shoppe, *Chem. & Ind.* 897 (1953).
[21] P. L. Julian, A. Magnani, E. M. Meyer et W. Cole, *J. Amer. Chem. Soc.* **70**, 1839 (1948).

brute $C_{23}H_{37}ON$, et un amino-alcool, l'*holadysamine* $C_{23}H_{37-39}ON$; des feuilles de l'espèce indienne, nous avons retiré la *kurchiphylline*, amine cétonique, de formule brute $C_{23}H_{35}O_2N$. Ces recherches n'en sont qu'à leur début. Elles montrent cependant que l'on ne retrouve pas dans les feuilles des *Holarrhena*, des alcaloïdes identiques à ceux isolés des écorces, et aussi qu'il peut exister de grandes différences entre deux espèces identiques, mais d'origines différentes.

Deux alcaloïdes très intéressants, ont été étudiés dans d'autres laboratoires: Dickel, Lucas et Phillamy[32] ont retiré de *Conopharyngia pachysiphon* le Dglucoside du 3β hydroxy-20α amino-pregna-5-ène, XXXIX, et Chatterjee[33] a établi la structure de la *chonemorphine*, XL, qui est le Δ^8, 3β amino-20 diméthylamino(5α)prégnène. Ce dernier alcaloïde a été retiré de *Chonemorpha fragrans* (Moon) Alston (*C. macrophylla* (Roxb.) G. Don) et de *Chonemorpha penangensis* Ridl.

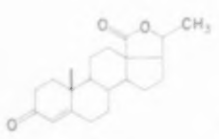
XXXIX

XL

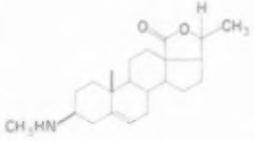
La découverte la plus significative, faite dans cette série de stéroïdes aminés, est celle de la *paravallarine*, isolée par Le Men, dans notre laboratoire, à partir de *Paravallaris microphylla* Pitard[34].

Les *Paravallaris* sont maintenant inclus dans le genre *Kibatalia* G. Don. Ce sont des Kibatalinées asiatiques, dont on connait deux espèces: *P. macrophylla* Pierre et *P. microphylla* Pitard, toutes deux originaires de la Cochinchine.

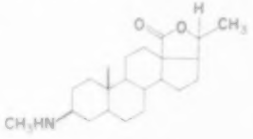
La *paravallarine*, XLI, est le (20 S)-3β méthylamino-20-hydroxy-18-oïque lactone (→20)pregna-5-ène. En effet, cet alcaloïde possède une fonction amine secondaire, une fonction lactone et une double liaison. Il peut être hydrogéné en dihydroparaval-



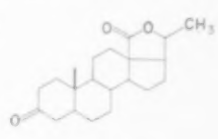
XLIV



XLI



XLII



XLIII

larine, XLII, dont la désamination selon Ruschig conduit à la céto-lactone XLIII, identique au produit recemment obtenu par Jeger[35] dans ses remarquables recherches sur la fonctionalisation du carbone 18 de la molécule stéroïde. La désamination de la paravallarine, élle-même conduit à la cétone conjuguée XLIV. La position de la double liaison est démontrée par Le Men, en utilisant les règles des différences de rotation moléculaire. La détérmination de la configuration 3β du groupe $NHCH_3$ est basée sur l'obtention, par hydrogénation catalytique de la double liaison, de dérivés de la série stéroïde A/B *trans*.

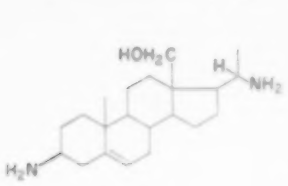
[32] D. Dickel, R. Lucas et H. B. McPhillamy, *J. Amer. Chem. Soc.* **81**, 3154 (1959).
[33] A. Chatterjee et B. Das, Abstracts of papers presented at I.U.P.A.C. Symposium, Australia (1960) p. 12.
[34] J. Le Men, *Bull. Soc. Chim. Fr.* 860 (1960).
[35] B. Kamber, G. Cainelli, D. Arigoni et O. Jeger, *Helv. Chim. Acta* **43**, 347 (1960).

STÉROÏDES AMINÉS NATURELS DES APOCYNACÉES

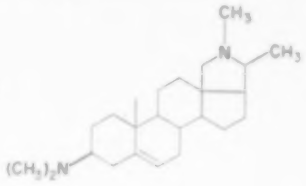
	Fonctions	F	$(\alpha)_D$	Origines	Références
5α-pregnane					
Funtumine	3α amino	126°	+95	*Funtumia latifolia*	4
$C_{21}H_{35}ON$	20-oxo				
Funtumidine	3α amino	182°	+10	*F. latifolia*	4
$C_{21}H_{37}ON$	20α hydroxy				
Funtuphyllamine A	3β hydroxy	173°	+13	*F. africana*	13
$C_{21}H_{37}ON$	20α amino				
Funtuphyllamine B	3β hydroxy	214°	+24	*F. africana*	13
$C_{22}H_{39}ON$	20α méthylamino			M. *bequaertiana*	21
Funtuphyllamine C	3β hydroxy	172°	+24	*F. africana*	13
$C_{23}H_{41}ON$	20α diméthylamino				
Funtumafrine B	3 oxo	160°	+43	*F. africana*	13
$C_{22}H_{37}ON$	20α methylamino				
Funtumafrine C	3 oxo	174°	+45	*F. africana* et *M. bequaertiana*	13
$C_{23}H_{39}ON$	20α diméthylamino				
Malouétine	3β, 20α bis	264° (picrate)		*Malouetia*	
$C_{21}H_{32}N_2^{++}, X_2^{--}$	triméthylammonium	chlorure +3		*bequaertiana*	21
Prégnène					
Holamine	Δ 4 ou 5, 3α amino	135°	+23	*Holarrhena floribunda*	29
$C_{21}H_{33}ON$	20 oxo				
Holaphyllamine	Δ⁵, 3β amino	260°	(ClH) +33	*H. floribunda*	28, 29
$C_{21}H_{35}ON$	20 oxo				
Holaphylline	Δ⁵, 3β méthylamino	128°	+23	*H. floribunda*	28
$C_{22}H_{37}ON$	20 oxo				
Gluco-alcaloïde	3β hydroxy, Δ⁵ 20α amino			*Conopharyngia pachysiphon*	32
Chonemorphine	3β amino, Δ⁵	145°		*Chonemorpha fragrans*	
$C_{28}H_{46}N_2$	20 diméthylamino		+25	*Ch. penangensis*	33
Paravallarine	Δ⁵, 3β méthylamino	181°	−52	*Paravallaris*	
$C_{23}H_{35}O_2N$	lactone 18–20α			*microphylla*	34
Structures non établies					
Iréhine	amino-alcool	163°	−30	*F. elastica*	3
$C_{23}H_{39}ON$					
Latifoline	amine tértiaire	135°	−4	*F. latifolia* (écorces)	3
$C_{23}H_{37}ON$	alcool				
Holadysine	amino-cétone	120°	−199	*H. antidysenterica* feuilles	
$C_{23}H_{37}ON$					
Holadysamine	amino-alcool	173°	−78	*H. antidysenterica* feuilles	
$C_{23}H_{37}ON$					
Kurchiphylline	amino-cétone	184°	−176	*H. antidysenterica* feuilles	
$C_{28}H_{55-57}O_2N$					
Malouphylline	amine tértiaire	259°	−10	*Malouetia*	
$C_{54}H_{80}O_2N_2$	acétamide cétone			*bequaertiana* feuilles	

Les pouvoirs rotatoires sont pris dans le chloroforme, sauf pour le chlorure de malouétine (eau) et le chlorhydrate d'holaphyllamine (méthanol)

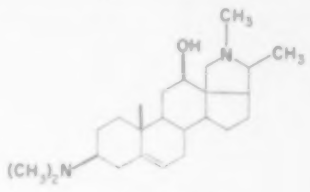
Nous voyons dans le tableau, que la classification chimique des différents stéroïdes aminés, permet de dégager toute une filiation continue, allant de la série du 5α-pregnane, avec des dérivés aminés en position 3, en position 20 et diaminés en 3 et en 20, à la série du pregna-5-ène présentant les mêmes substitutions, pour aboutir à la



XLV



XLVI



XLVII

paravallarine, alcaloïde oxygéné en position 18. La paravallarine est ainsi l'intermédiaire entre les bases stéroïdes simples et les dérivés de la conanine. On peut la considérer comme un précusseur de l'*holarrhimine*, XLV, elle-même précurseur de la *conessine*, XLVI. Le terme le plus complexe de toute cette série est, jusqu'à présent, constitué par l'*holarrhénine*, XLVII, et par ses esters: *holafrine* et *holarrhétine*.[36]

Nos remerciements vont au Professeur M.-M. Janot auquel mon nom est associé, dans nos communes recherches, depuis 25 années, au Professeur J. Le Men pour ses beaux travaux sur la paravallarine, ainsi qu'a nos collaborateurs: Mme C. Conreur, Mlle F. Lainé, MM. Q. Khuong-Huu, A. Cavé et Longevialle.

[36] H. Rostock et E. Seebeck, *Helv. Chim. Acta* **41**, 11 (1958).

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ÜBER DIE KONSTITUTION DES C-CURARINS*[1]

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Zusammenfassung—Durch Abbaureaktionen und Analyse von Kernresonanz-spektren wird für C-Curarin die Formel I abgeleitet: die Halochromiereaktionen des Alkaloids werden diskutiert.

Abstract—By chemical degradation and analysis of nmr spectra formula I for C-curarine was deduced; the halochromic reactions of the alkaloid are briefly discussed.

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In einer früheren Mitteilung[2] wurden für C-Curarin, $C_{40}H_{44-46}ON_4^{++}$, einem der Hauptalkaloide aus Calebassencurare, die alternativen Formeln I und Ia vorgeschlagen. Diese Vorschläge beruhten u.a. auf der Beobachtung, dass durch partielle Quartärnisierung von bisnor-C-Curarin (II) ein kristallisiertes, offenbar einheitliches nor-C-Curarin-monochlormethylat entsteht, das mit Methyljodid-[^{14}C], gefolgt von Anionenaustausch, ein C-Curarin-[^{14}C]-dichlorid gibt, welches bei der säurekatalysierten Hydrolyse C-Fluorocurarin mit der halben molaren Radioaktivität des eingesetzten C-Curarins-[^{14}C] liefert. Der daraus gezogene Schluss, dass C-Curarin aus zwei gleichen Hälften aufgebaut ist, gilt natürlich nur dann, wenn das erwähnte nor-C-Curarin-monochlormethylat tatsächlich eine einheitliche Verbindung und nicht ein 1 : 1 Gemisch zweier nahe verwandter Isomeren darstellt.

Durch hydrierenden Hofmann'schen Abbau geht C-Curarin in die bitertiäre sog. Tetrahydrobase[3,4] VII, $C_{40}H_{48-50}ON_4$, über, in der der zentrale Teil der Curarinmolekel dem U.V.- und I.R.-Spektrum nach zu schliessen unverändert geblieben zu sein scheint.[4] Beim Erwärmen, auch unter sorgfältigem Sauerstoffausschluss, mit verd. Salzsäure bildet sich daraus eine Indolinbase VIII,[2] $C_{40}H_{48}O_2N_4$, in der, wie aus ihrem U.V.-Spektrum (Indolin) und ihrem I.R.-Spektrum (keine NH—, OH—, $\diagup\!\!\diagdown C{=}N-$ oder $-N{=}C\diagup\!\!\diagdown$ -Banden; intensive Aetherbande bei 8,56μ) und weiteren Eigenschaften folgt, die beiden Sauerstoffatome ätherartig gebunden vorliegen. Danach enthält der zentrale Teil der C-Curarinmolekel neben der Aethergruppierung *zwei* Doppelbindungen, d.h. dem Alkaloid ist die den Strukturformeln I oder Ia entsprechende Summenformel $C_{40}H_{44}ON_4^{++}$ zuzuschreiben.

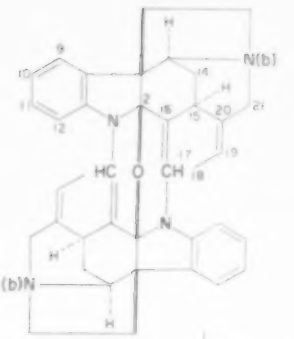
* Vorläufige Mitt.: 48. Mitt. über Curare-Alkaloide; die ausführliche Mitt. wird in den Helv. Chim. Acta erscheinen.

[1] 47. Mitt.: W. Arnold, M. Hesse, H. Hiltebrand, A. Melera, W. von Philipsborn, H. Schmid und P. Karrer, *Helv. Chim. Acta* **44**, 620 (1961).

[2] W. von Philipsborn, W. Arnold, J. Nagyvàry, K. Bernauer, H. Schmid und P. Karrer, *Helv. Chim. Acta* **43**, 141 (1960).

[3] H. Wieland, H. J. Pistor und K. Bähr, *Liebigs Ann.* **547**, 140 (1941).

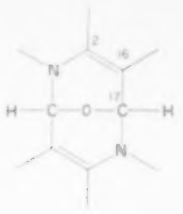
[4] W. von Philipsborn, H. Schmid und P. Karrer, *Helv. Chim. Acta* **38**, 1067 (1955); (Formel II dieser Arbeit); Diss. W. von Philipsborn, Universität Zürich 1956; V. Boekelheide, O. Ceder, M. Natsume und A. Zürcher, *J. Amer. Chem. Soc.* **81**, 2256 (1959).



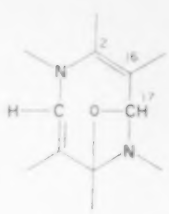
I: C-Curarin —N(b)—CH_3

II: bisnor-C-Curarin

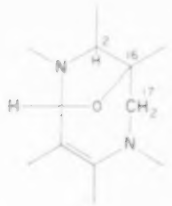
XV: II mit NO_2-Gruppen in den Stellungen 10 und 10'



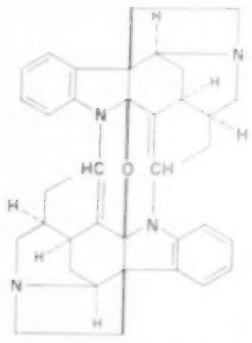
Ia



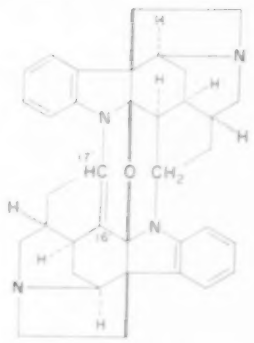
Ib



Ic



III : bisnor-Tetrahydrocurarin



IV : bisnor-Hexahydrocurarin

In einer kürzlich erschienenen Arbeit[5] diskutieren Th. Wieland, Reinshagen und Fritz für C-Curarin die um 2 H reichere Bruttoformel und die Strukturformel Ic. Bei der Salzsäure-Spaltung des Alkaloids fanden nämlich die Autoren neben C-Fluorocurarin in sehr kleiner Menge 18-Desoxy-Wieland-Gumlich-aldehyd. Bei der katalytischen Hydrierung von C-Curarin in verd. Schwefelsäure resultiert ferner ein leider nur wenig charakterisiertes Dodekahydroderivat, in dem neben den zwei Aethylidendoppelbindungen die drei Doppelbindungen *eines* aromatischen Ringes und eine zusätzliche Doppelbindung abgesättigt sein sollen. Die aus diesen Befunden gezogenen Schlüsse scheinen uns aber nicht zwingend zu sein: C-Fluorocurarin geht nämlich beim Erwärmen mit verd. Salzsäure in Desformylfluorocurarin und Ameisensäure über,[6] die z.B. einen geringen Teil des Fluorocurarins zum 18-Desoxy-Wieland-Gumlich-aldehyd reduzieren könnte. Desformylfluorocurarin wurde von uns bei der Säurespaltung von C-Curarin neben C-Fluorocurarin stets nachgewiesen.[7] Endlich

[5] Th. Wieland, H. Reinshagen und H. Fritz, *Naturwissenschaften* **48**, 50 (1961).
[6] K. Bernauer, W. Arnold, Ch. Weissmann, H. Schmid und P. Karrer, *Helv. Chim. Acta* **43**, 717 (1960).
[7] J. Nagyváry, unveröffentlichte Versuche.

schliesst die Bildung von "unsymmetrischen" Hydrierungsprodukten eine aus zwei gleichen Hälften aufgebaute C-Curarinformel nicht aus, da bei Absättigung z.B. einer zentralen Doppelbindung die Molekel "unsymmetrisch" wird und bei weiterer Hydrierung zu gleichfalls "unsymmetrischen" Hydrierungsprodukten führen könnte.

Weitere, nachfolgend aufgeführte Experimente bestätigen für C-Curarin die Bruttoformel $C_{40}H_{44}ON_4^{++}$ und führen zur Strukturformel I.

(1) Hydrierung von dem gegenüber $NaBH_4$ und $LiAlH_4$ beständigen bisnor-C-Curarin[8] (II) mit PtO_2 in Eisessig (Aufnahme 2 Mol H_2) lieferte das kristallisierte bisnor-Tetrahydro-curarin (III), $C_{38}H_{42}ON_4$,[9] in dem nur die beiden Aethylidenseitenketten abgesättigt sind (kein Acetaldehyd bei der Ozonolyse), und das hinsichtlich Farbreaktionen, U.V.- und I.R.-Spektren (Tabelle 1) mit II weitgehend übereinstimmt. Bei der Hydrierung von II in Eisessig mit einem grossen Ueberschuss von Platinoxyd, wobei man 3,5–4 Mol H_2 aufnehmen liess, entstanden weitere Hydrierungsprodukte, aus denen sich durch Chromatographie III, sowie in kleiner Menge das kristallisierte bisnor-Hexahydro-curarin IV, $C_{38}H_{44}ON_4$,[10] das kristallisierte bisnor-Octahydro-curarin V, $C_{38}H_{46}ON_4$, sowie wasserstoffreichere kristallisierte Diindoline abtrennen liessen. Letztere konnten aus Materialmangel nicht näher untersucht werden.

Bisnor-Hexahydro-curarin (IV) mit blauvioletter Cer(IV)-sulfat- und schmutzig violetter Salpetersäure-Farbreaktion zeigt ein U.V.-Spektrum (Tabelle 1, Fig. 1), das durch

TABELLE 1. U.V. SPEKTREN (IN 96-PROZ. ALKOHOL) UND I.R. SPEKTREN

Substanz	λ_{max} in mμ (log ε)	λ_{max} in μ
C-Curarin-dichlorid·5 H_2O (I)	260 (4·41); 296 (4·07)	6·04; 6·24 (KBr)
Bisnor-C-Curarin (II)	264 (4·42); 300 (4·14)	6·03; 6·23 (CCl_4)
Bisnor-Tetrahydro-curarin (III)	261 (4·37); 300 (4·07)	6·04; 6·24 (CCl_4)
Bisnor-Hexahydro-curarin (IV)	256 (4·10); 291 (4·34); Schulter 313 (4·03)	6·07; 6·22; 6·25 ($CHCl_3$)
Bisnor-Octahydro-curarin (V)	264 (4·52); 311·5 (3·81)	6·24 (CCl_4)
Tetrahydrobase (VII)	258 (4·38); 290 (4·07)	5·99; 6·20 (CCl_4)

Ueberlagerung eines Indolin- und eines "halben" C-Toxiferin-I-chromophors zustande kommen kann.[11] Im I.R. fehlen NH- und OH-Banden;[12] während die Toxiferin-Alkaloide und I, II und III jeweils eine einzige "Indolin"-bande zeigen, tritt im Spektrum von IV eine wenig getrennte Doppelbande bei 6·22 und 6·25 μ auf. Auffällig ist die im Vergleich zu II und III hohe Intensität und Verschiebung der Enaminbande

[8] H. Schmid, A. Ebnöther und P. Karrer, *Helv. Chim. Acta* **33**, 1486 (1950); W. von Philipsborn, H. Schmid und P. Karrer, *Ibid.* **39**, 913 (1956).

[9] Von allen neu beschriebenen Substanzen liegen korrekte Analysen vor; durch CH-Analysen lässt sich kein Entscheid zwischen den angegebenen und den um 2 H reicheren Formeln treffen.

[10] Neben dieser Verbindung bildete sich noch in sehr kleiner Menge eine hinsichtlich der Farbreaktion, und Spektren sehr ähnliche Substanz, in der die Seitenketten nur unvollständig hydriert sind.

[11] 22,23-Dehydro-19,20-dihydrostrychnin zeigt λ_{max} 278 mμ (log ε = 4·18) und eine Schulter bei 309 mμ (log ε = 3·86).

[12] Die Spektren wurden auch in einer 1 cm Quarzzelle in CCl_4 mit einem Beckman Gerät IR-7 aufgenommen. Im Bereich von 2·7–4·0 μ waren weder OH-, noch NH-Banden sichtbar, auch nicht nach Zusatz von wenig D_2O. In derselben Weise verhielt sich die Indolinbase VIII.

nach 6·07 μ. Die Verbindung wird durch Erhitzen mit Lauge (0·2 N KOH; 95°) ebensowenig verändert wie II. Bei der Hydrierung entsteht neben weiter abgesättigten Stoffen in kleiner Menge V (durch U.V.-Spektrum und Dünnschichtchromatogramme nachgewiesen).

Bisnor-Octahydro-curarin (V) zeigt im U.V. (Tabelle 1) ein zweifaches, langwelliges Indolinchromophor; im I.R. fehlen wiederum OH- und NH-Banden.[12] Es gibt die für $N_{(a)}$-alkylierte Indoline typische carminrote Cer(IV)-sulfat- und mit Salpetersäure eine rotviolette Farbreaktion. Auch V lässt sich weiter hydrieren. Erwähnt sei noch, dass bei der Hydrierung von III die Verbindungen IV und V höchstens in Spuren gebildet werden; III ist somit nicht direktes Zwischenprodukt.

Da, wie unter Punkt 4 gezeigt wird, bei der Hydrierung von II zu V (und damit auch zu IV) keine Emdespaltung zwischen den $N_{(b)}$-Atomen und C-21 bzw. C-21′ eingetreten ist, und da auf Grund der I.R.-Spektren von IV und V eine Hydrogenolyse einer $N_{(a)}$-C oder C—O Bindung ausgeschlossen werder darf, folgt, dass in IV der Sauerstoff wie in II ätherartig gebunden, also eine C=C-Bindung des zentralen Ringes abgesättigt sein muss. Die Verbindung enthält aber auf Grund der U.V.- und I.R.-Spektren noch mindestens eine Enaminbindung. Daraus lässt sich schliessen, dass C-Curarin und II und III *zwei* zentrale Doppelbindungen enthalten, womit die früher von uns für das Alkaloid angegebene Summenformel $C_{40}H_{44}ON_4^{++}$ erhärtet wird. Das für bisnor-C-Curarin (II) massenspektrometrisch ermittelte Molekulargewicht beträgt 566 in Übereinstimmung mit der Formel $C_{38}H_{38}ON_4$ für II, bzw. der angegebenen Formel für C-Curarin.

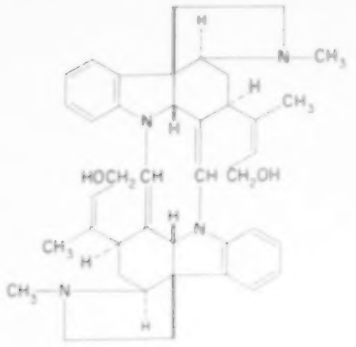
(2) Die früher erwähnte Indolinbase,[13] $C_{40}H_{48}O_2N_4$ welche die Partialformel VIII besitzt, zeigte in konz. Salzsäure ein U.V.-Spektrum, dessen Extinktion zwei Indoleninium-chromophoren entspricht, [λ_{max} 243 mμ (log $\varepsilon = 4{\cdot}16$); 248 mμ (log $\varepsilon = 4{\cdot}13$) und 315 mμ (log $\varepsilon = 4{\cdot}13$)] (Vgl. hiezu das U.V.-Spektrum von C-Alkaloid D in konz. Salzsäure);[14] VIII liess sich aus einer solchen Lösung unverändert zurückgewinnen. Reduktion der Verbindung in konz. Salzsäure mit Zink bei −15° gab nach Chromatographie eine amorphe Base IX, $C_{40}H_{52}N_4$, mit Indolinabsorption [λ_{max} 255 mμ (log $\varepsilon = 4{\cdot}38$) und 305 mμ (log $\varepsilon = 3{\cdot}76$)] und keiner NH-Bande im Infrarot; sie wurde als kristallisiertes Dimethojodid, $C_{42}H_{58}N_4J_2$, und Dihydrochlorid, $C_{40}H_{54}N_4Cl_2{\cdot}H_2O$, $[\alpha]_D = -274°$ (MeOH), charakterisiert. Letzteres gab bei der modifizierten Chromsäureoxydation nur Essigsäure und nahm mit Platinoxyd in Eisessig ca. 2·4 Mole H_2 unter Bildung einer amorphen, im Hochvakuum destillierbaren Base X, $C_{40}H_{56}N_4$ ($[\alpha]_D = -299°$ ($CHCl_3$); kein NH im I.R.) auf, die ein kristallisiertes Dihydrochlorid ($[\alpha]_D = -244°$ (MeOH)) gab.

C-Toxiferin-I-dichlorid gab mit Pd/C in 0·1 N alkoholischer Kalilauge unter Aufnahme von 2 H_2 das bis-Emdeprodukt XI, $C_{40}H_{48}O_2N_2$ (Smp. 174–176°; $[\alpha]_D = -937°$ ($CHCl_3$); I.R.-Bande bei 6·04 μ (KBr); U.V.-Spektrum sehr ähnlich demjenigen des C-Toxiferins I). Durch Behandeln von XI mit 60-proz. Bromwasserstoffsäure und Zink bei −15°, Zugabe frischer Bromwasserstoffsäure, Stehenlassen während 20 Std. bei 20°, Verdünnen mit Wasser und Reduktion mit Zinkstaub bei 20°[15] resultierte nach Chromatographie eine amorphe Base XII, $C_{40}H_{52}N_4$ (U.V.- und I.R.-Spektren: Di-indolin), die ein kristallisiertes Dihydrochlorid, $C_{40}H_{54}N_4Cl_2$

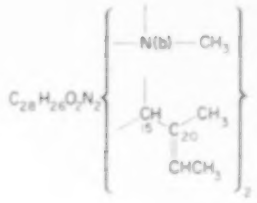
[13] Vgl.[12]

[14] H.-D. Schroeder, H. Hiltebrand, H. Schmid und P. Karrer, *Helv. Chim. Acta* **44**, 34 (1961).

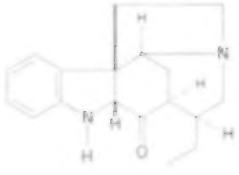
[15] Vgl. K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid und P. Karrer, *Helv. Chim. Acta* **42**, 201 (1959).



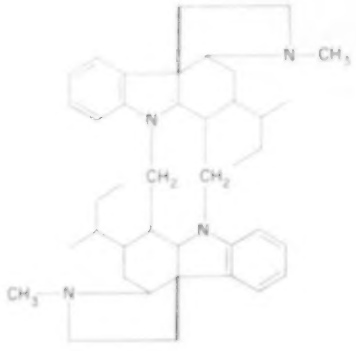
XI



VIII



XIV



X, XIII

($[\alpha]_D = -241°$ (MeOH)), gab. Das Dihydrochlorid in Eisessig lieferte mit Wasserstoff und Platinoxyd (Abbruch der Hydrierung nach Aufnahme von 2·2 Molen H_2) und nach Chromatographie eine amorphe, im Hochvakuum destillierbare Base XIII, $C_{40}H_{56}N_4$ ($[\alpha]_D = -274°$ ($CHCl_3$)), die durch ein kristallines Dihydrochlorid ($[\alpha]_D = -227°$ (MeOH)) charakterisiert wurde. Die U.V.-Spektren der Basen X und XIII sowie ihrer Dihydrochloride sind identisch; die I.R.-Spektren (in CCl_4; Nujol und KBr) zeigen keine signifikanten Unterschiede. Die Nichtidentität der beiden Produkte folgt aber aus den etwas verschiedenen Drehungen und geringen Unterschieden in den Cer(IV)-sulfat-Farbreaktionen und R_f-Werten in Dünnschichtchromatogrammen. Auch die Debye-Scherrer Diagramme der beiden Dihydrochloride zeigen zwar eine Reihe gemeinsamer Linien, sind aber nicht identisch. Wir glauben, aus diesen Befunden aber doch den Schluss ziehen zu dürfen, dass X und XIII dieselbe Struktur besitzen und sich nur durch Stereoisomerie oder durch einen verschiedenen Gehalt an Stereoisomeren unterscheiden. C-Curarin und C-Toxiferin I hätten demnach dasselbe Gerüst.

(3) Ozonisierung[16] von bisnor-Tetrahydro-curarin (III) in Methanol, Behandeln mit aktivem Zink, Säurehydrolyse, gefolgt von SO_2-Reduktion allfällig noch vorhandener $N_{(b)}$-Oxyde, gab Strychanon (XIV),[16] das durch Mischprobe, spez. Drehung und I.R.-Spektren identifiziert wurde. Der Befund spricht für die 16,17-bzw.

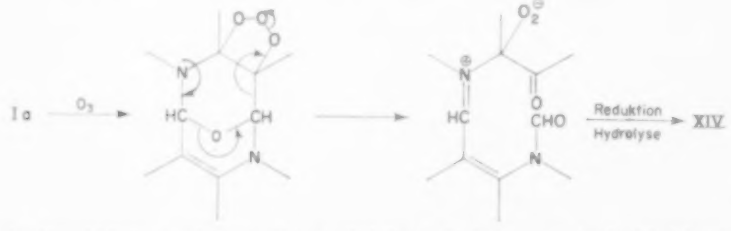
[16] Ch. Weissmann, O. Heshmat, K. Bernauer, H. Schmid und P. Karrer, *Helv. Chim. Acta* **43**, 1165 (1960).

16′,17′-Stellung der zentralen Doppelbindung(en) in C-Curarin;[17] das bei der Ozonolyse zunächst zu erwartende 2-Hydroxystrychanon wird mit Zink zu XIV reduziert.

(4) Im 60 MHz-Kernresonanzspektrum[18] ($CDCl_3$) zeigt bisnor-C-Curarin (II) das bei 319 c/s zentrierte Quartet (J = 7 c/s) der beiden Vinylprotonen an C-19 und C-19′ und das Dublett der beiden Methylgruppen bei 109 und 102 c/s. Das durch mehrere elektronische Integrationen bestimmte Verhältnis von "Vinyl"- und "Aromaten"- protonen beträgt 2 : 9·9 ± 0·2. Aus der Aromatenregion sticht ein Dublett bei 400 c/s mit J = 1·2 c/s heraus. Ein breites, zwei Protonen entsprechendes Signal bei 220 c/s dürfte von den beiden Methinprotonen an C-15 und C-15′ stammen.[19] Signale von C-2,2′-Methinprotonen, die je nach ihrer Umgebung zwischen 235–318 c/s[1,20] zu erwarten sind, fehlen. Im Spektrum von bisnor-Tetrahydro-curarin (III) ($CDCl_3$) erscheint in der Aromatenregion wiederum ein herausragendes Dublett (J = 1 c/s) bei 400 c/s; Signale von Seitenketten-Vinylprotonen fehlen. Die Tatsache, dass zwischen 205 und 389 c/s keine Absorption auftritt, bestätigt erneut die Abwesenheit von C-2,2′-Methinprotonen. Durch die Absättigung der beiden seitenständigen Doppelbindungen wird das Signal der beiden C-15,15′-Methinprotonen nach höheren Feldstärken hin verschoben. Die beiden Methylgruppen geben ein für solche Aethylgruppen zu erwartendes, bei 65 c/s zentriertes Multiplett. C-Curarin-dichlorid in D_2O zeigt folgende Signale: ein Quartett bei 375 c/s (J = 6 c/s) der beiden Vinylprotonen an C-19,19′, ein bei 135 c/s zentriertes Dublett (J = 6 c/s) der beiden Methylgruppen, ein Singlett bei 215 c/s der beiden $-\overset{|}{\overset{+}{N}}_{(b)}-CH_3$-Gruppen und innerhalb der Aromatensignale ein etwas Feinstruktur zeigendes Singlett bei 442 c/s. Das durch mehrere Integrationen bestimmte "Vinyl-/Aromaten"-protonenverhältnis wurde zu 2 : 9·8 ± 0·2 gefunden. Das Spektrum von bisnor-Octahydro-curarin (V) in $CDCl_3$ zeigt die nur 7·8 ± 0·1 Aromatenprotonen entsprechenden Signale an; es fehlt in dieser Region eine herausstechende Bande. Das für die Aethylgruppen charakteristische Signal ist bei 48 c/s zentriert. Im Gegensatz zu III gibt diese Verbindung bereits komplexe Signale ab ca. 235 c/s gegen höhere Magnetfeldstärken.

Von besonderem Interesse sind die in den Spektren von II, III und C-Curarin als Dubletten (J ~ 1 c/s) bzw. als Singlett auftretenden Signale bei 400 c/s bzw. 442 c/s, die nur von annähernd in den Ebenen der magnetisch anisotropen Benzolkerne liegenden, den Strukturelementen I, Ia oder Ib zugehörenden C-17,17′-Protonen stammen können.

[17] Gegen dieses Argument könnte allenfalls der Einwand erhoben werden, dass sich auch nach folgendem Mechanismus aus einer Substanz der Struktur Ia ein Mol XIV gebildet haben könnte:



[18] Chemische Verschiebungen relativ zu Tetramethylsilan = 0 als interner Standard bei den Aufnahmen in $CDCl_3$ bzw. externer Standard bei der Aufnahme von C-Curarindichlorid in D_2O.

[19] An derselben Stelle erscheint beim bisnor-C-Toxiferin I ein zwei Protonen entsprechendes Signal.[1]

[20] C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery und L. F. Johnson, *Experientia* **16**, 532 (1960).

Ganz abgesehen davon, dass es sehr unwahrscheinlich ist, dass die verschiedenen C-17,17′-Protonen in Ib praktisch dieselbe chemische Verschiebung zeigen, ergibt die Analyse des NMR-Spektrums von 10,10′-Dinitro-C-curarin-dichlorid (XV) (Fig. 2), $C_{80}H_{82}O_5N_6Cl_2 + 2H_2O$[21] in D_2O,[22] dass auch die *unmittelbare* Umgebung der beiden Benzolkerne in der Curarinmolekel identisch sein muss. Das Spektrum lässt die erwarteten Signale der zwei Seitenkettenvinylprotonen (bei 379 c/s zentriertes Quartett mit J = 6·5 c/s), der zwei $-\overset{|}{\overset{+}{N}_{(b)}}-CH_3$-Gruppen (Singlett bei 217 c/s) und der beiden Methylgruppen (bei 139 c/s zentriertes Dublett mit J = 6·5 c/s) erkennen. Die Aromatenregion zeigt zwei Gruppen von Signalen, die relativ zu den Vinylprotonen C-19,19′ 8·2 ± 0·2 Protonen entsprechen. Das von zwei Protonen stammende Dublett bei kleinster Feldstärke, 521 c/s (J ~ 1,5 c/s), ist den Protonen an C-9 und C-9′ zuzuordnen; sie zeigen die erwartete Grösse der Spin–Spin-Kupplung mit den hiezu meta-ständigen Protonen an C-11,11′. Hierauf folgt ein bei 507 c/s zentriertes Dublett (zwei Protonen) mit J = 9 c/s; die einzelnen Banden zeigen Feinaufspaltung mit J ~ 1·5 c/s. Ein korrespondierendes Dublett mit J = 9 c/s (zwei Protonen) ist bei 445 c/s zentriert und zeigt sehr geringe, nicht aufgelöste Feinaufspaltung (J < 1 c/s). Das Dublett 507 c/s kommt somit von den beiden zu den Nitrogruppen orthoständigen Protonen an C-11 und C-11′, die mit den Protonen an C-9,9′ (J ~ 1,5 c/s) und den benachbarten Protonen an C-12 und C-12′ (J = 9 c/s) kuppeln. Die Signale der letzteren Protonen erfahren durch die Einführung der beiden Nitrogruppen relativ zu ihrer Lage im Spektrum des C-Curarins die geringste Verschiebung.[23] Die 10,10′-Stellung der Nitrogruppen in XIV ist somit bewiesen. Uebrig bleibt in der Aromatenregion ein zwei Protonen entsprechendes Singlett bei 458 c/s, das nur von Vinyl- oder Methinprotonen an C-17,17′ herrühren kann. Im Spektrum von C-Curarin tritt dieses Singlett wie erwähnt bei 442 c/s auf. Nach unseren Erfahrungen wird der Charakter der Aromatenmultiplette stark durch verschiedene Substitution an C-17,17′ beeinflusst.[1,24] Die Analyse des Spektrums von XV zeigt aber, dass in der Aromatenregion nur Signale von Protonen*paaren* vorkommen. Wenn ferner das im Spektrum von C-Curarin vorhandene Singlett 442 c/s von zwei Arten von Protonen herrühren würde, wäre es wenig wahrscheinlich, dass die Einführung der Nitrogruppen die Signale dieser Protonen in genau der gleichen Weise verschieben und diese wiederum als Singlett in Erscheinung treten lassen würde. Curarinformeln wie Ib und Ic, die nicht aus zwei gleichen Hälften aufgebaut sind, fallen somit weg. In den Kernresonanzspektren von C-Toxiferin-I-dichlorid (D_2O) bzw. bisnor-C-Toxiferin I ($CDCl_3$) treten die beiden Vinylprotonen an C-17,17′ als Singlette bei 412 bzw. 375 c/s auf.[1] Im Spektrum von Caracurin V[14] ($CDCl_3$) erscheinen die Amino-acetalprotonen an C-17,17′ als Dublett bei 281 c/s (J ~ 2 c/s[25]). Es scheint uns wenig wahrscheinlich,

[21] Das gelb gefärbte, prächtig kristallisierende Dinitro-dichlorid wurde aus dem bereits von H. Wieland und Mitarbeitern[3] bereiteten Dinitro-C-curarin-dinitrat durch Ionenaustausch gewonnen. Es zeigt keine Cer(IV)-sulfat-Reaktion und keine Halochromie-färbung mit konz. Salzsäure, wohl aber mit konz. Schwefelsäure (violett).

[22] Als interne Eichbande diente die Wasserbande, deren Position 306 ± 2 c/s sich auf einen externen Tetramethylsilan-Standard bezieht.

[23] Vgl. J. A. Pople, W. G. Schneider und H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance* Seite 258 *ff*. McGraw-Hill, New York (1959).

[24] Siehe auch später erscheinende Mitteilungen.

[25] Die Grösse der Spin-Spin-Kupplung dieser Protonen mit denjenigen an C-16,16′ spricht für die unter[14] angegebene Konfiguration der Zentren 17,17′ in Caracurin V: *cf.* H. Conroy in *Advances in Organic Chemistry, Methods and Results* Vol. II, Seite 310–311, Interscience, New York (1960).

dass die Signale solcher Protonen in II und III, falls die beiden Substanzen im zentralen Teil der Formel Ib entsprächen, eine Verschiebung bis 400 c/s erleiden würden. Die geringe Verschiebung der C-17,17′-Protonensignale von C-Curarin, II und III um ca. 25–28 c/s nach kleineren Feldstärken im Vergleich zur Lage der entsprechenden

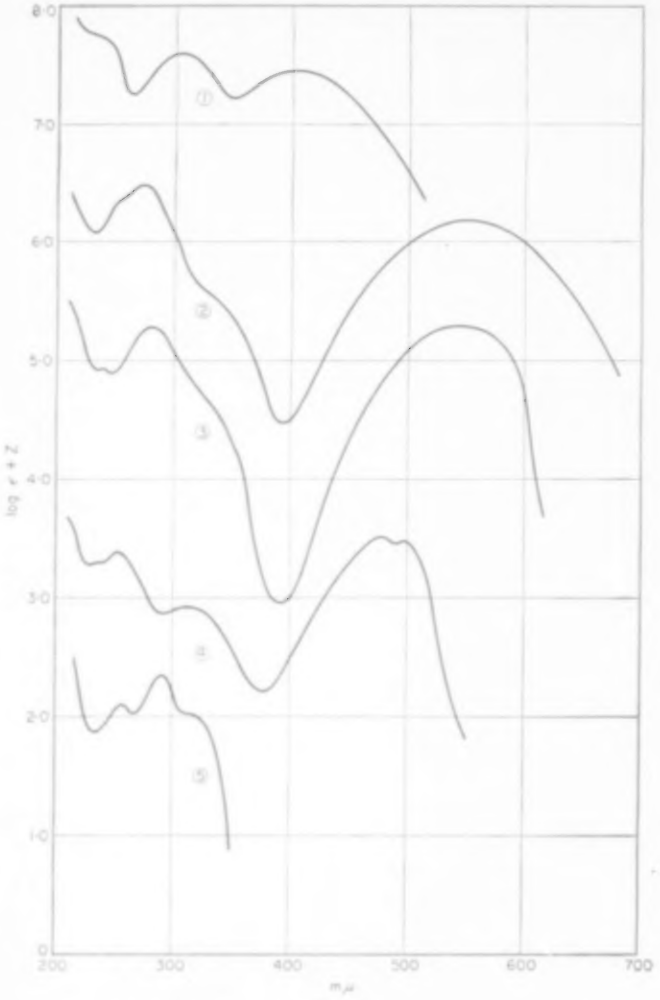


FIG. 1.
Kurve 1—bisnor-Tetrahydro-curarin in konz. Schwefelsäure
$c = 6{\cdot}36 \cdot 10^{-5}$ (M = 570·8) $z = 3{\cdot}60$
Kurve 2—bisnor-Tetrahydro-curarin in 70-proz. Schwefelsäure (Gew.%)
$c = 5{\cdot}25 \cdot 10^{-5}$ (M = 570·8) $z = 2{\cdot}20$
Kurve 3—bisnor-Hexahydro-curarin in 70-proz. Schwefelsäure (in konz. H_2SO_4 gelöst und auf 70-proz. H_2SO_4 verdünnt)
$c = 3{\cdot}02 \cdot 10^{-5}$ (M = 572·8) $z = 1{\cdot}00$
Kurve 4—bisnor-Hexahydro-curarin in 70-proz. Schwefelsäure (direkt gelöst und nach 2½ Std. gemessen)
$c = 3{\cdot}20 \cdot 10^{-4}$ (M = 572·8) $z = -0{\cdot}80$
Kurve 5—bisnor-Hexahydro-curarin in 96-proz. Alkohol
$c = 2{\cdot}86 \cdot 10^{-5}$ (M = 572·8) $z = -2{\cdot}00$

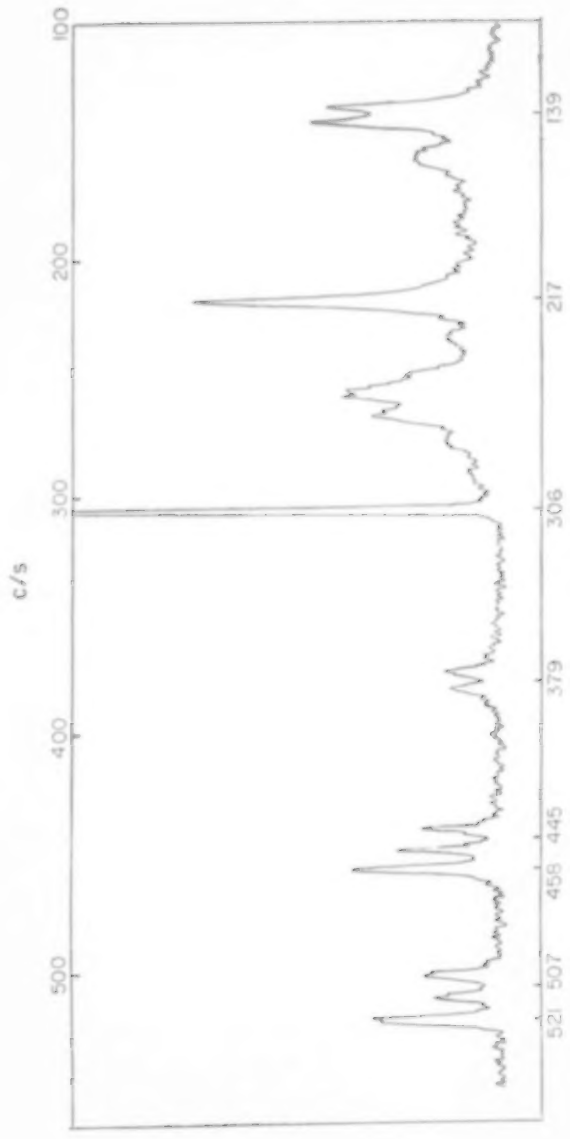
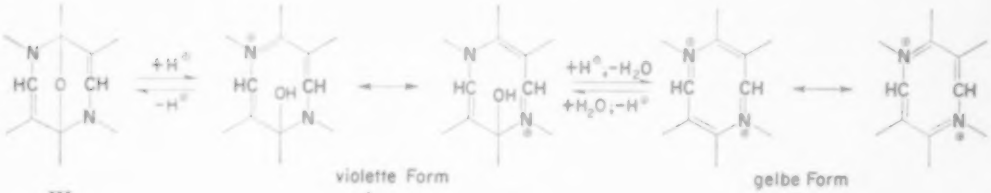


FIG. 2. Kernresonanz-spektrum von 10,10'-Dinitro-C-Curarin-dichlorid (XV).

Banden in C-Toxiferin I und bisnor-C-Toxiferin I kann durch die Anwesenheit des Aethersauerstoffs bedingt sein. Die Kernresonanzspektren machen daher für C-Curarin von den beiden alternativen Formeln I und Ia die erstere wahrscheinlicher.[26]

(5) Auffällig am C-Curarin und seinen Derivaten II und III sind Halochromieerscheinungen auf Zusatz von starker Säure. Bisnor-Tetrahydro-curarin (III), das wir in dieser Hinsicht etwas genauer untersucht haben, zeigt intensiv violette Halochromie im Bereich von ca. 40–85-proz. Schwefelsäure;[27] in konz. Schwefelsäure löst sich das Alkaloid wie C-Curarin mit gelber Farbe auf. Beim Verdünnen mit Wasser tritt zuerst Violettfärbung, dann Entfärbung auf. Aus der verdünnt schwefelsauren Lösung lässt sich III in quantitativer Ausbeute unverändert (U.V.- und I.R.-Spektren; Dünnschichtchromatogramme) zurück gewinnen. Die violette Farbe in 70-proz. Schwefelsäure (Spektrum: Fig. 1, Kurve 2) ist unserer Ansicht nach auf die säurekatalysierte Umwandlung des Curarinchromophors in das Cyanin A zurückzuführen, das in konz. Schwefelsäure Wasser unter Ausbildung eines neuartigen 1,5-Di-azoniumcyclooctatetraen-chromophors B (Spektrum: Fig. 1, Kurve 1) abspaltet. 10,10′-



III A B

Dinitro-C-curarin-dichlorid liegt auch in konz. Schwefelsäure aus verständlichen Gründen nur in der violetten Farbe vor.

Bisnor-Hexahydro-curarin kann die Formel IV zugewiesen werden.[28] Seine U.V.-Absorption (Fig. 1, Kurve 5) kommt offensichtlich, wie schon früher erwähnt, durch Ueberlagerung eines Indolin- und eines "halben"-Toxiferin-I-chromophors zustande. Während der zentrale Teil in I, II und III starr ist, ist dieser Teil in IV in ähnlicher Weise flexibel wie in C-Toxiferin-I und seinen Abkömmlingen, wodurch eine bessere Ueberlappung der Orbitale des Enaminsystems möglich ist. Das von diesem System herrührende Hauptmaximum, welches von I, II, III bei 260–264 mμ gegeben wird (Tabelle I), liegt in guter Uebereinstimmung mit demjenigen der bisnor-Tetrahydro-dihydrotoxiferine[1] bei 291 mμ. Hydrierung einer zentralen Doppelbindung in der Struktur Ia hingegen würde die sterischen Verhältnisse des verbleibenden Enaminsystems nicht verändern.

Auch IV gibt Halochromiereaktionen.[29] In 70-proz. Schwefelsäure oder konz. Salzsäure löst sich die Base mit intensiver rotoranger Farbe (Spektrum: Fig. 1, Kurve 4), die beim Verdünnen mit Wasser wieder verschwindet; IV lässt sich daraus zum grossen Teil unverändert zurückisolieren. In konz. Schwefelsäure tritt Violettfärbung

[26] Die geringe Aufspaltung der C-17,17′-Protonensignale in den Spektren von II und III ist durch allylische,1,3-Kupplung mit den Protonen an C-15,15′ bedingt. Im Falle einer Formel Ia wären stets reine Singlette zu erwarten.

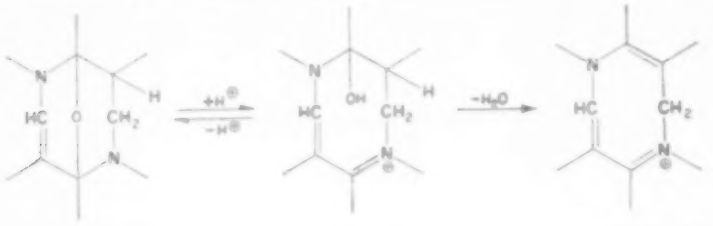
[27] Gewichtsprozente.

[28] Leider lag von der Verbindung zur Aufnahme eines Kernresonanz-spektrums nicht genügend Substanz vor.

[29] Diese Halochromiefärbungen sind Zeitreaktionen; maximale Absorption erhält man nach einigen Std. Stehen bei 20°.

ein; diese bleibt auch beim Verdünnen auf 70-proz. Schwefelsäure und mehr *erhalten* (Spektrum: Fig. 1, Kurve 3); erst beim Abpuffern auf ca. pH 5 beobachtet man rasche Entfärbung und das Spektrum des Ausgangsmaterials.

Diese Erscheinungen lassen sich wie folgt formulieren:



IV rotorange Form violette Form

Das Spektrum der violetten Form ist ähnlich demjenigen der rotorangen Form und stimmt sehr gut mit dem Spektrum der violetten Form des bis-nor-Tetrahydrocurarins (III) überein. Die Tatsache, dass die violette Form von IV nicht mehr protonisiert wird, veranlasst uns, die diprotonisierte gelbe Form des bisnor-Tetrahydro-curarins (III) wie oben angeführt zu formulieren. Der bei Erniedrigung der Acidität des Milieus ohne weiteres erfolgende Aetherringschluss wird in der rotorangen Form von IV und der violetten Form von III durch die bereits vorhandene Hydroxylgruppe bedingt; die violette Form von IV wird erwartungsgemäss rasch erst bei relativ hohem pH hydratisiert und in IV umgewandelt.[30]

Schwierigkeiten begegnet die Formulierung von bisnor-Octahydro-curarin (V). Der Stoff besitzt, wie erwähnt, keine OH- oder NH-Gruppe, zeigt aber in 0·2 N wässerig-alkoholischer Kalilauge eine reversible Rotverschiebung der Indolin-maxima nach 270 mμ ($\log \varepsilon = 4{\cdot}50$) und 315 m$\mu$ ($\log \varepsilon = 3{\cdot}89$); die Base lässt sich aus der alkalischen Lösung zurückgewinnen. Derartige Laugeverschiebungen werden als charakteristisch für in Nachbarstellung zum Stickstoff hydroxylierte Indoline angesehen.[31] In kalter 5 N-Salzsäure wird V an $N_{(a)}$ monoprotonisiert; nach dem Erhitzen mit konz. Salzsäure (1 Std., 60°, Hochvakuum) werden Maxima bei 242 mμ ($\log \varepsilon = 4{\cdot}02$); 245 m$\mu$ ($\log \varepsilon = 4{\cdot}01$) und 305 m$\mu$ ($\log \varepsilon = 3{\cdot}86$) (konz. Salzsäure) beobachtet, die *einem* Indoleninium-chromophor entsprechen; das zweite $N_{(a)}$-Atom muss in protonisierter Form vorliegen. Dieses Verhalten ist von einer Formel mit 2,2′-Aetherbrücke nicht zu erwarten.[32]

Einer genaueren Untersuchung bedürfen auch die mit Alkali durch Hofmann- und Emdeabbau aus C-Curarin erhältlichen bitertiären Basen,[2–4] in denen die $N_{(b)}$-C-21,21′-Bindungen gelöst sind. Diese Stoffe geben nicht mehr die typischen Halochromie-farbreaktionen; sie zeigen Absorptionsverschiebungen bei der Protonisierung und Quartärnisierung der $N_{(b)}$-Atome und säurekatalysierte Umwandlungen in Di-indolin-diätherbasen, obwohl auf Grund der ausgeprägten Alkalistabilität von II, III und IV, sowie der U.V.- und I.R.-Spektren der zentrale Teil unverändert geblieben zu sein scheint.

[30] Die Halochromieerscheinungen werden von uns noch genauer studiert.

[31] H. Volz und Th. Wieland, *Naturwissenschaften* **44**, 376 (1957); H. Fritz und Th. Wieland, *Liebigs Ann.* **611**, 268 (1958); K. Bernauer, H. Schmid und P. Karrer, *Helv. Chim. Acta* **41**, 673 (1958).

[32] Vielleicht handelt es sich um ein Umlagerungsprodukt mit einem 1-Oxo-3-azacyclobutan-System. In diesem Zusammenhang sei noch erwähnt, dass C-Curarin-dichlorid bei der Perhydrierung in N/8 Schwefelsäure mit einem starken Ueberschuss von Platinoxyd 11 Mole Wasserstoff aufnimmt.

Wir danken den Herren Dr. A. Melera, Varian Forschungslaboratorium Zürich, und Dr. C. von Planta, F. Hoffmann-La Roche Basel, für Aufnahme der Kernresonanzspektren und wertvolle Diskussionen, Drs. C. Wildman und H. M. Fales, National Institutes of Health, Bethesda, für die Bestimmung der I. R.-Spektren von IV, V und VIII und Drs. A. Fürst, A. Boller und H. Els, F. Hoffmann-La Roche Basel, für die Überlassung wertvoller Präparate. Vielmals zu danken haben wir auch Herrn Prof. F. Laves, Zürich, für die Debye-Scherrer Aufnahmen, Herrn Prof. K. Biemann, M.I.T., Cambridge, für die Molekulargewichtsbestimmung von II, dem Schweizerischen Nationalfonds für wissenschaftliche Forschung und der eine von uns (J. N.) für ein Monsanto-Stipendium.

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PREPARATION AND PERACID OXIDATION OF 2-(*p*-DIMETHYLAMINO)-STYRYL-PYRIDINE

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Abstract—The title compound is obtained by reduction of its 1-oxide, prepared in fair yield by condensation of 2-picoline-1-oxide and *p*-dimethylamino-benzaldehyde in pyridine in the presence of KOH. The results of the stepwise oxidation by perbenzoic acid show that the oxygen atom adds first to the amino nitrogen, appearing to indicate that the interaction effects between the dimethylamino group and the pyridine ring are small.

IN substituted pyridines electronic interaction between an electron-donor substituent and the pyridine nucleus, is greatest when the substituent is bonded directly to the nucleus, but is decreased to a surprising extent when the substituent is bonded to the pyridine through a system of conjugated double bonds.

The absorption spectra of the three *p*-dimethylamino-phenylazo-pyridines[1] are very similar; only the 4-isomer exhibits a small bathochromic shift. Examination of the absorption spectra of the isomeric phenylazopyridines,[2] very similar to each other and almost identical with that of the azobenzene, indicates the existence of a small degree of conjugation between the phenylazo-group and the pyridine nitrogen.

This report concerns the behaviour, with respect to the oxidation by organic peracids, of the 2-(*p*-dimethylamino)-styryl-pyridine, in which the —CH=CH— group is substituted for the azo group between the pyridine and the substituted-phenyl-group, and also describes a convenient method of preparation of the starting base.

The condensation of α-picoline with *p*-dimethylamino-benzaldehyde was reported by Parker and Furst[3] who effected the condensation in toluene in the presence of piperidine acetate as catalyst. They observed, however, the preferential formation of an unidentified compound corresponding to the empirical formula $C_{23}H_{27}N_3$. This same compound was obtained also not only when 2-picoline base was replaced by its 1-oxide, but even when no heterocyclic was used in the reaction. Apparently, this compound is formed from the condensation of the aldehyde with piperidine under the conditions used by the above.

By the condensation of *p*-dimethylamino-benzaldehyde with 2-picoline-1-oxide, the above authors obtained (together with the unidentified product) 2-(*p*-dimethylamino)-styryl-pyridine-1-oxide, isolated with difficulty and in a maximum yield of 13 per cent after 47 hours of reaction time.

Jerchel *et al.*,[4] studying the reaction between α-picoline and benzaldehyde, stated that the reaction is best carried out in a mixture of a mole of acetic anhydride and a mole of acetic acid per mole of picoline and 1·2 moles of benzaldehyde, with exclusion

[1] L. Pentimalli, *Tetrahedron* **9**, 194 (1960).
[2] L. Pentimalli, *Gazz. Chim. ital.* **90**, 1203 (1960).
[3] E. D. Parker and A. Furst, *J. Org. Chem.* **23**, 201 (1958).
[4] D. Jerchel and H. E. Heck, *Liebigs Ann.* **613**, 171 (1958).

of air. In basic medium, on the other hand, the best results were obtained in methanol, by the addition of 0·2 mole of piperidine per mole of picoline derivative and 1·4 moles of benzaldehyde. With piperidine acetate or potassium acetate, as condensing agents, the yields decrease. Furthermore, Jerchel *et al.*[4] stated that 2- and 4-picoline undergo condensation only in acidic medium.

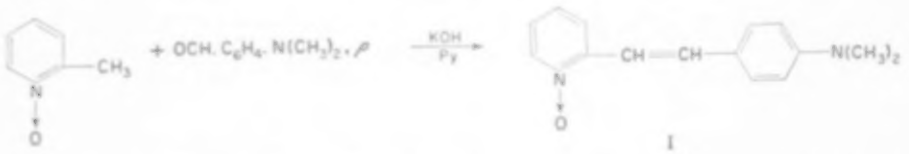
If the picoline 1-oxides and benzaldehyde are allowed to react in acidic medium, no condensation occurs. In methanol or s-butanol, in the presence of piperidine, only N,N'-benzylidene-di-piperidine is formed. The styryl-pyridine 1-oxides are obtained instead from 2- and 4-picoline 1-oxides with potassium methoxide in methanol, in 56 per cent yield,[4] according to an earlier method by Katritzky,[5] who obtained 2-styryl-pyridine-1-oxide in 22 per cent yield.

Katritzky also prepared[6] in the γ-series, 4-(*p*-dimethylamino)-styryl-pyridine (12 per cent yield) by condensation in acidic medium, of aldehyde (0·08 mole) with 4-picoline (0·08 mole) in acetic anhydride (0·20 mole) by a 30 hours reflux under nitrogen, and 4-(*p*-dimethylamino)-styryl-pyridine-1-oxide (11 per cent yield) from 4-picoline-1-oxide and *p*-dimethylamino-benzaldehyde, by the above method.[6]

Our research has allowed the development of a method of preparation of the 2-(*p*-dimethylamino)-styryl-pyridine by reduction of its 1-oxide, obtained (in fair yield) by condensation in basic medium.

The condensation of the picoline base with aromatic aldehydes occurs, as mentioned, in acidic medium; in the case of *p*-dimethylamino-benzaldehyde, whose reactivity is often particularly low, the maximum yields are little better than 10 per cent. The use of additional catalysts, of other stronger acids, or of more vigorous conditions, does not improve the results and often leads only to resinous products without recovery of the starting materials.

The condensation of the picoline 1-oxide, which we have seen gives rather low



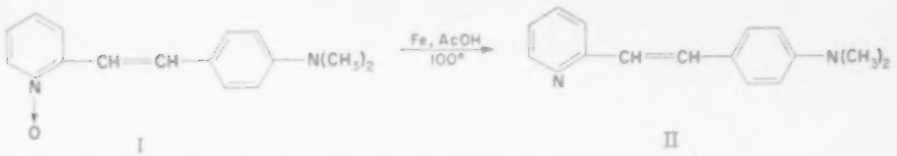
I

yields with potassium methoxide in methanol, is effected much better, as we have found, in anhydrous pyridine in the presence of powdered potassium hydroxide, under a 3–6 hour reflux. From 4-picoline-1-oxide and *p*-dimethylamino-benzaldehyde, 4-(*p*-dimethylamino)-styryl-pyridine-1-oxide was obtained in 78 per cent yield after 3 hours of reflux. From 2-picoline-1-oxide and aldehyde the corresponding 2-styryl-derivative I was obtained in 56 per cent yield. Yields are generally lower with 2-picoline than with the 4-isomer.[4]

The separation of the styryl derivative is readily carried out by decomposing the reaction mixture with water and washing the formed precipitate with a little cold acetone. In the condensation with KOH, in the presence or absence of piperidine, secondary products were not apparent.

By treating the N-oxide with iron and acetic acid at 100°,[7] only oxygen is lost and

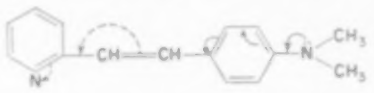
[5] A. R. Katritzky and A. M. Monro, *J. Chem. Soc.* 150 (1958).
[6] A. R. Katritzky, D. J. Short and A. J. Boulton, *J. Chem. Soc.* 1516 (1960).
[7] H. J. den Hertog, *Rec. Trav. Chim.* **69**, 472 (1950), 4-amino-pyridine from 4-nitro-1-oxide.



I II

2-(*p*-dimethylamino)-styryl-pyridine II is thus formed in 50–60 per cent yield. The ethylenic double bond, therefore, remains intact, which is different from the observation with the 1,2-bis-α-quinolyl-ethylene N,N′-dioxide, whose olefinic bond is reduced yielding 1,2-bis-α-quinolil ethane, under these conditions.[8]

Peracid oxidation of this styryl derivative was studied because, also in this case, the relative electron density on the amino– and pyridine–nitrogens will depend on the extent of the electronic interaction through the conjugated chain.



The experimental results indicate that for mono-oxidation of the 2-styryl-derivative an almost colourless compound is obtained to which must be assigned the amino oxide structure on the basis of U.V. absorption.

The 2-(*p*-dimethylamino)-styryl-pyridine base presents (Fig. 1) an intense main band at 368 mμ due to the conjugation of the dimethylamino group with the rest of

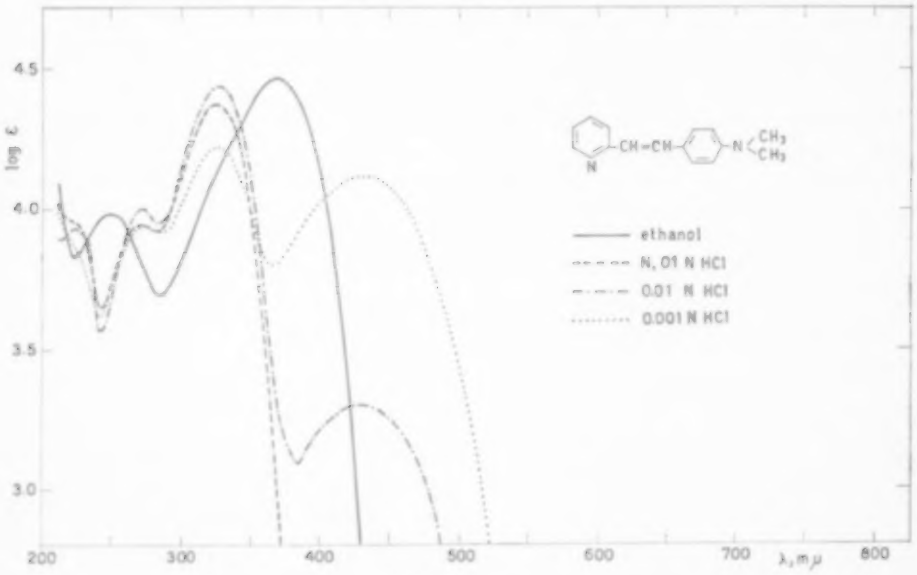


FIG. 1.

the molecule. In strongly acidic medium both pyridine– and amino–nitrogens undergo protonation. The protonation of the dimethylamino group impedes the conjugative interaction of the substituent and the absorption decreases, assuming spectral

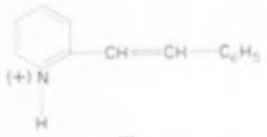
[8] M. Colonna, *Gazz. Chim. Ital.* **90**, 1179 (1960).

characteristics of the 2-styryl-pyridine in acidic medium. In the case of the protonated amino-derivative the absorption is even lower than that of the 2-styryl-pyridine in

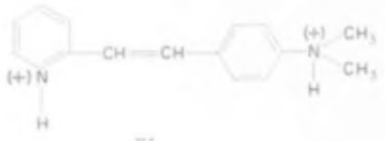
TABLE I. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (log ε) IN THE ABSORPTION SPECTRA OF 2-(*p*-DIMETHYLAMINO)-STYRYL-PYRIDINE IN ETHANOL AND IN AQUEOUS-ETHANOLIC HCl

	λ_1	λ_2	λ_3	λ_4
2-(*p*-dimethylamino)-styryl-pyridine	250(3·98)	—	368(4·46)	—
2-(*p*-dimethylamino)-styryl-pyridine N, 0·1 N HCl	224∼	272(3·94)	324(4·37)	—
2-(*p*-dimethylamino)-styryl-pyridine 0·01 N HCl	224(3·92)	272(3·99)	324(4·43)	424(3·30)
2-(*p*-dimethylamino)-styryl-pyridine 0·001 N HCl	224∼	272(3·94)	324(4·22)	424(4·11)
2-styryl-pyridine	228(4·02)	—	310(4·40)	—
2-styryl-pyridine N HCl	...	280(3·91)	336(4·42)	—

acidic medium since, in the latter, the conjugation of the styryl group was conditioned by the N-protonation, while in the former the electron withdrawing effect of the



III



IV

quaternary nitrogens at the extremes of the chain opposes the individual effect of each.

In weakly acidic medium an equilibrium between the bis-cation IV and the mono-cation V at the pyridine nitrogen occurs, which shifts toward the mono-cation as the

V

acid concentration decreases, as shown by the bathochromic shift of the spectrum with respect to that of the free base in ethanol. Protonation at the pyridine nitrogen rather than that at the amino nitrogen is due to the higher resonance stabilisation.

The product of mono-oxidation presents a spectrum (Figs. 2 and 3) almost identical to that of the unsubstituted 2-styryl-pyridine, giving evidence that here also the conjugative effect of the substituent has disappeared. In acidic medium there is a bathochromic shift, as observed with the 2-styryl-pyridine. This clearly shows, then, that the first oxygen atom is bonded to the amino-nitrogen rather than the pyridine nitrogen.

No solvent effect has been found; the mono-oxidation, performed either in chloroform or in carbon tetrachloride, always led to the same results.

VI

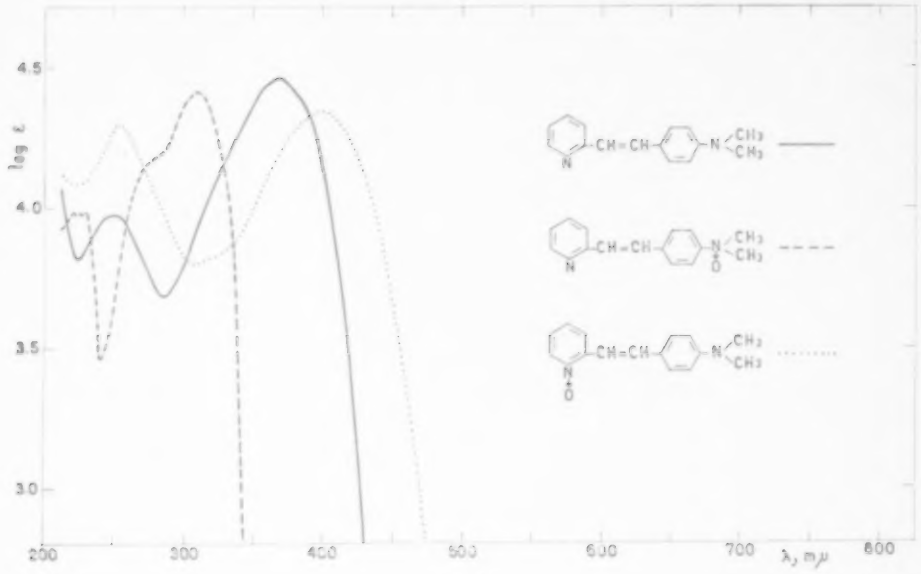
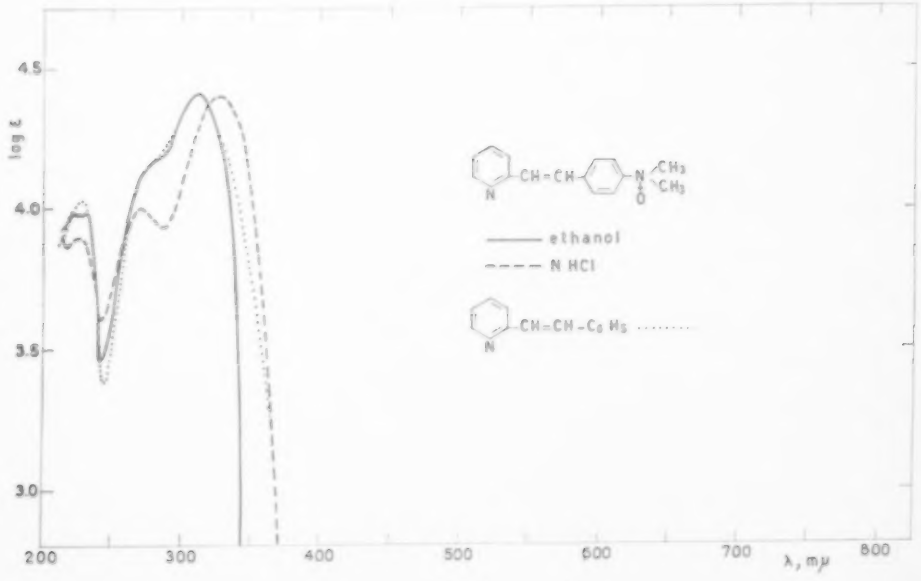

log ε
4.5
4.0
3.5
3.0
200
300
400
500
600
700
800
λ, mμ

FIG. 2.


log ε
4.5
4.0
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200
300
400
500
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700
800
λ, mμ
ethanol
N HCl

FIG. 3.

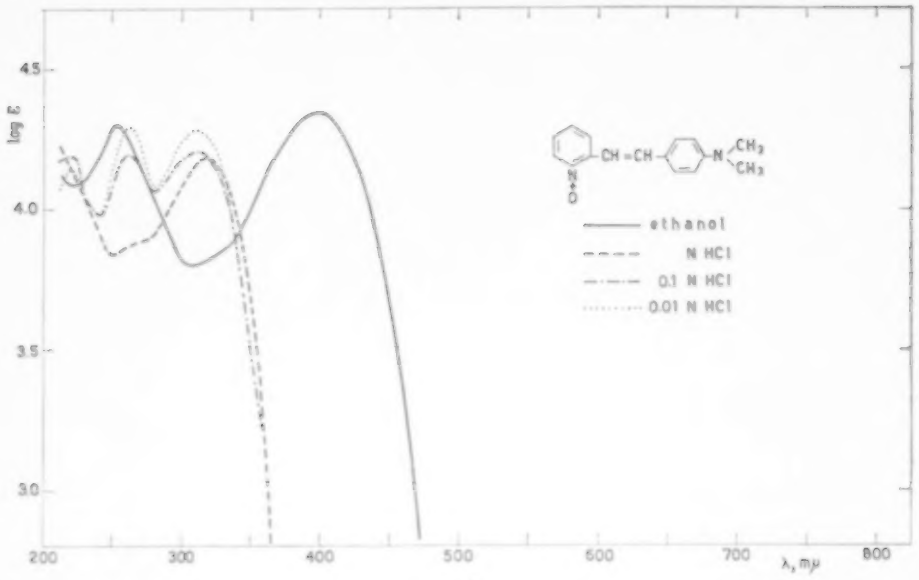


FIG. 4.

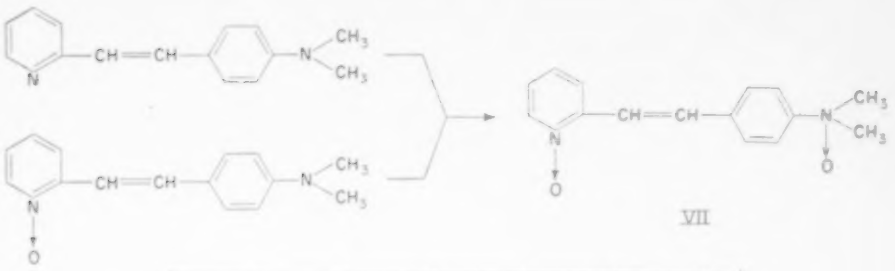
TABLE 2. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (log ε) IN THE ABSORPTION SPECTRA OF 2-(*p*-DIMETHYLAMINO)-STYRYL-PYRIDINE AND RELATED N-OXIDES IN ETHANOL

	λ_1	λ_2	λ_3
2-(*p*-dimethylamino)-styryl-pyridine	250(3·98)	—	368(4·46)
2-(*p*-dimethylamino)-styryl-pyridine 1-oxide	252(4·30)		398(4·34)
2-(*p*-dimethylamino)-styryl-pyridine amino-oxide	226(3·98)	—	310(4·41)
2-(*p*-dimethylamino)-styryl-pyridine bis-oxide	232(3·96)	270(4·34)	318(4·39)
2-styryl-pyridine	228(4·02)	—	310(4·40)
2-styryl-pyridine 1-oxide	...	272(4·31)	320(4·38)

TABLE 3. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (log ε) IN THE ABSORPTION SPECTRA OF 2-(*p*-DIMETHYLAMINO)-STYRYL-PYRIDINE-1-OXIDE IN ETHANOL AND IN AQUEOUS-ETHANOLIC HCl

	λ_1	λ_2	λ_3
2-(*p*-dimethylamino)-styryl-pyridine-1-oxide	252(4·30)		398(4·34)
2-(*p*-dimethylamino)-styryl-pyridine-1-oxide 0·01 N HCl	220(4·14)	262(4·29)	312(4·28)
2-(*p*-dimethylamino)-styryl-pyridine-1-oxide 0·1 N HCl	218(4·18)	260(4·19)	312(4·20)
2-(*p*-dimethylamino)-styryl-pyridine-1-oxide N HCl	...	—	318(4·17)

The 1-oxide derivative, prepared by direct synthesis, presents instead (Figs. 2 and 4) a bathochromic shift of the main band, as is the general case with conjugated substituted pyridine 1-oxides. The characteristic band of the pyridine 1-oxide group (usually at 260–270 mμ) probably remains masked by the broad band in the same



VII

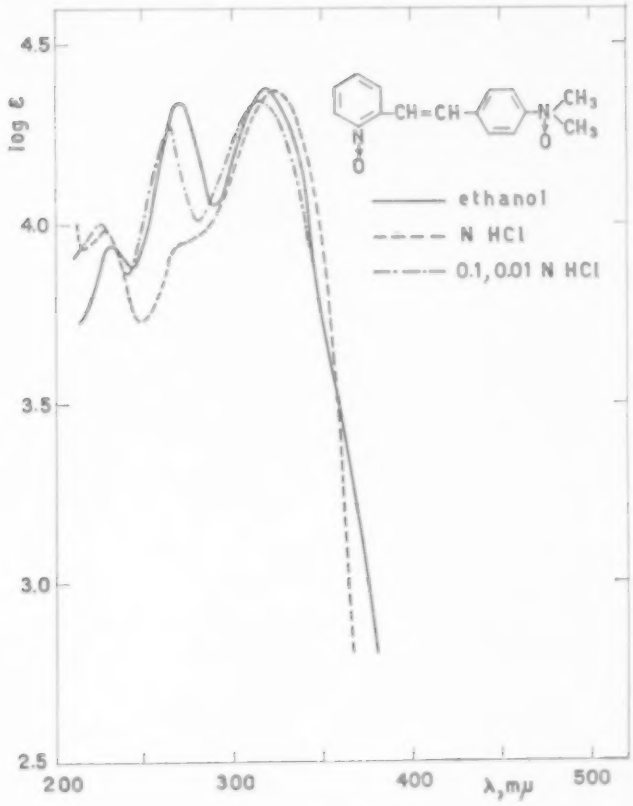


FIG. 5.

region, with λ_{max} at 252 mμ. In 0·01 N HCl the dimethylamino group is protonated, with subsequent disappearence of the electronic interaction of the substituent and corresponding reversion of the absorption curve to that of the unsubstituted 2-styryl-pyridine 1-oxide (Fig. 7).

As acidity is increased even the N → O group tends to become protonated, indicated by a weakening of the original conjugation band which completely disappears in N HCl, as is the general case with aromatic N-oxides.

The product of bis-oxidation, obtained by complete oxidation either of the base or mono-oxide, contains two atoms of oxygen, one bonded to the amino–nitrogen and

the other to the pyridine–nitrogen. Indeed (Fig. 5), the λ_{max} of conjugation in the higher wavelength region corresponds to that of the unsubstituted 2-styryl-pyridine (Fig. 6) and, moreover, the new band at 270 mμ, corresponding to that observed with pyridine N-oxides, is reduced to a mere inflection in strongly acidic medium.

From the results of the step-wise oxidation of the 2-(*p*-dimethylamino)-styryl-pyridine it is concluded that the first oxygen atom is bonded only to the amino–nitrogen

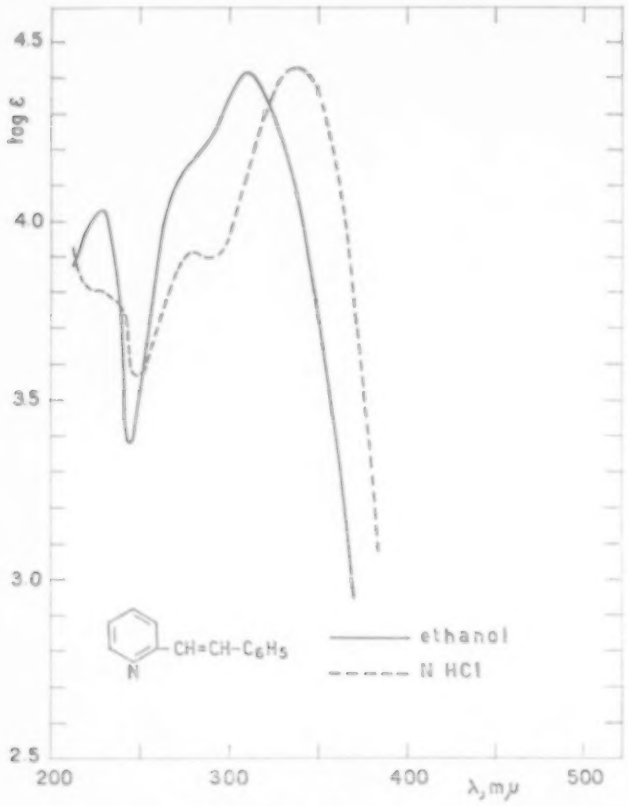


FIG. 6.

and the second oxygen to the pyridine–nitrogen. Here also, therefore, as seen before in the corresponding azo-derivative, the electron density remains highest at the amino–nitrogen relative to that at the pyridine–nitrogen. Katritzky[9] showed, on the other hand, that for the styryl- and ethynyl-derivatives the interaction effects between the substituent and the pyridine ring are small in every case with respect to the effects observed[10] for the substituents directly bonded to the pyridine ring.

EXPERIMENTAL

2-(p-*Dimethylamino*)*styryl-pyridine* 1-*oxide* (I). A solution of 2-picoline 1-oxide (2·2 g, 0·020 mole) and *p*-dimethylamino-benzaldehyde (4·3 g, 0·028 mole) in anhydrous pyridine (6 ml) was added with potassium hydroxide (1·0 g) and gently refluxed for 6 hr; yellow crystals separated on the walls of the

[9] A. R. Katritzky and P. Simmons, *J. Chem. Soc.* 1511 (1960).
[10] H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.* **77**, 4441 (1955).

flask. The mixture was cooled, poured into cold water (100 ml) and stirred for 20 min. The brown precipitate was collected, washed with water, dried, shaken with cold acetone (30 ml) and filtered, yielding bright yellow long needles (ethanol), 2·8 g (yield 57%), m.p. 200–201° (lit.[3]: 200–201°).

2-(p-*Dimethylamino*)-*styryl-pyridine* (II). To the dark-red solution of I (4 g) in glacial acetic acid (80 ml), at 90°, iron powder (6 g) was gradually added, under vigorous stirring, during 20 min, keeping the temperature at 100°. Fifteen minutes after the completion of the addition, the mixture was cooled and made strongly alkaline by the addition of aqueous NaOH. The precipitate was collected, washed

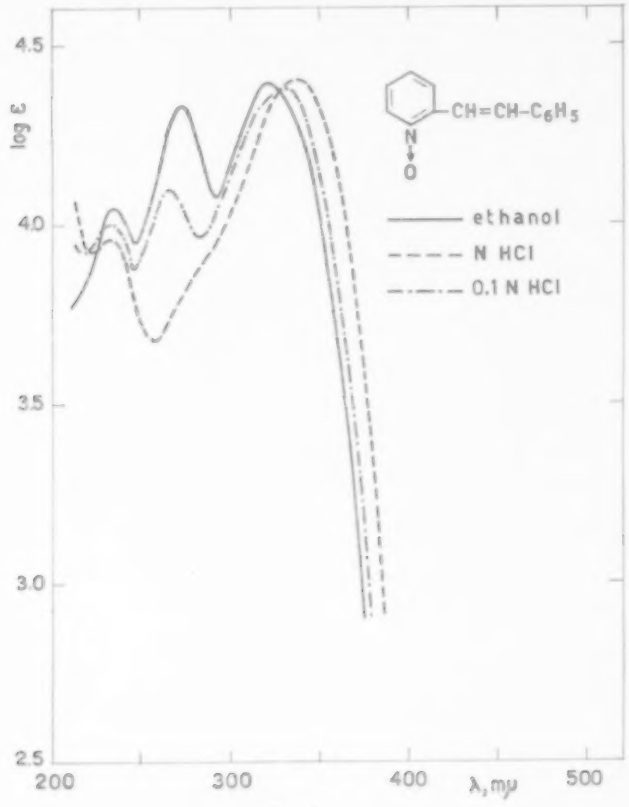


FIG. 7.

with water, dried, powdered, extracted with hot benzene (two 50 ml portions) and the benzene evaporated: crude residue, m.p. 136–138°. Recrystallization (methanol) afforded 2·2 g (yield 60%), m.p. 139° (lit.[3]: 142–143°).

Mono-oxidation of II. To a solution of II (1·0 g) in chloroform (8 ml), at 15°, a solution of perbenzoic acid (0·7 g, 1·2 moles) in chloroform was slowly added. After standing overnight the peracid was completely reacted, and the mixture was shaken with saturated sodium carbonate solution, dried (anhydrous sodium carbonate), filtered and the chloroform evaporated. Shining colourless plates (benzene), m.p. 100° dec. (Found: N, 10·34; Calc. for $C_{15}H_{16}N_2O$: N, 10·14%), identified as 2-(*p*-dimethylamino-N-oxide)-styryl-pyridine (VI).

The same procedure was followed in carrying out the reaction in carbon tetrachloride, with exclusion of chloroform from the reaction mixture. Only the above amino oxide was isolated and characterized.

Bis-oxidation of II. To a solution of II (1·0 g) in chloroform (10 ml), at 15°, a solution of perbenzoic acid (1·7 g, 3 moles) in chloroform was slowly added. By the above procedure, 2-(*p*-dimethylamino-N-oxide)-styryl-pyridine-1-oxide (VII), light yellow prisms (pyridine), m.p. 148°, was obtained (Found: N, 9·60; Calc. for $C_{15}H_{16}N_2O_3$: N, 9·58%).

Oxidation of I. To a solution of I (4 g) in chloroform (40 ml), at 15°, a solution of perbenzoic acid (2·76 g, 1·2 moles) in chloroform was slowly added. By the above procedure, yellow prisms (pyridine), m.p. 148°, were obtained, found identical with the bis-oxide VII.

2-*Styryl-pyridine*. Prepared by condensation of α-picoline (4·7 g, 1 mole) and benzaldehyde (4·6 g, 1·2 moles) in glacial acetic acid (2·9 ml) and acetic anhydride (4·8 ml).[4] White plates (ligroin b.p. 60–80°) m.p. 89–90° (lit.[4]: 89–90°) were obtained.

2-*Styryl-pyridine*-1-*oxide*. Prepared (1) by condensation of 2-picoline-1-oxide (2·2 g, 0·020 mole) and benzaldehyde (3 g, 1·2 moles) with potassium methoxide (5 ml of a 10% methanolic solution) in methanol (5 ml)[4] or (2) by oxidation of the base (7·2 g) by 36% hydrogen peroxide (6·3 ml) in glacial acetic acid (25·7 ml).[4,5] Almost colourless prisms (benzene) were obtained, m.p. 162–163° (lit.[4]: 162–163°).

Ultra-violet-visible absorption spectra. The absorption spectra were determined in 95% ethanol and aqueous-ethanolic HCl with a Beckman Model DU Quartz spectrophotometer.

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THE FORMATION OF 3(OR 5)-METHYLCYCLOPENT-2-EN-2-OL-1-ONE* FROM ACETONE

G. I. FRAY
Research Laboratory, Shell Chemical Company Ltd., Egham, Surrey

(*Received* 27 *January* 1961)

Abstract—The original observation that 3(or 5)-methylcyclopent-2-en-2-ol-1-one (I) was formed (in low yield) by the treatment of glycidaldehyde with acetone in the presence of aqueous alkali, and speculations concerning the reaction mechanism, led to the realization that the reaction could also be carried out with glyceraldehyde. This suggested an explanation for the previously known formation of I by drastic alkali-treatment of carbohydrates.

THE treatment of glycidaldehyde (II)[3] with acetone and aqueous alkali afforded, in low yield, a crystalline solid of composition $C_6H_8O_2$, which was found to be identical with the known 3(or 5)-methylpent-2-en-2-ol-1-one (I).[1,2] This compound is a minor product of the destructive distillation of wood,[4] and has also been obtained from wood by the action of hot aqueous alkali under pressure.[5] It has previously been synthesized (a) by dehydrogenative cyclization of 3,4-dihydroxyhexa-1,5-diene (III) with copper,[6]

Ib Ia Ic II

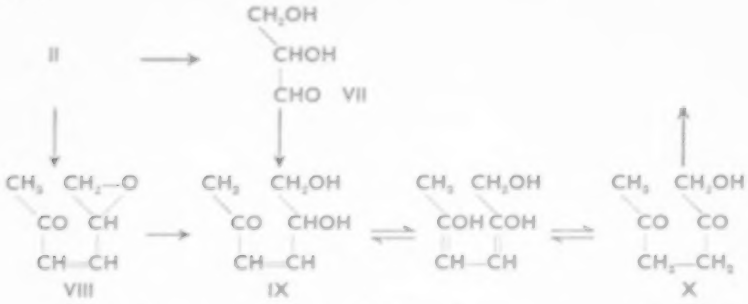
III IV V VI

(b) from 2-methylcyclopentanone (IV) by chlorination and subsequent hydrolysis of the resulting dichloro-derivative,[7] (c) from 3,5-diethoxycarbonylcyclopentan-1,2-dione (V) by methylation followed by ketonic hydrolysis,[8] and (d) by epoxidation of 3-methylcyclopent-2-en-1-one (VI) and isomerization of the resulting epoxide with boron trifluoride.[9]

* The mono-enol form in which 3-methylcyclopentan-1,2-dione (Ia) exists was originally thought to have the structure of 3-methylcyclopent-2-en-2-ol-1-one (Ib).[1] Later investigators,[2] however, preferred to formulate the compound as 5-methylcyclopent-2-en-2-ol-1-one (Ic).

[1] C. A. Rojahn and F. Rühl, *Arch. Pharm.* **264**, 211 (1926).
[2] G. Hesse and K. Breig, *Liebigs Ann.* **592**, 120 (1955).
[3] G. B. Payne, *J. Amer. Chem. Soc.* **81**, 4901 (1959).
[4] J. Meyerfeld and C. Ohlgart, *Chem. Z.* **36**, 549 (1912).
[5] T. Enkvist, B. Alfredsson, M. Merikallio, P. Pääkkönen and O. Järvelä, *Acta Chem. Scand.* **8**, 51 (1954).
[6] G. Dupont and E. Urion, *C.R. Acad. Sci., Paris* **197**, 158 (1933); E. Urion, *Ann. Chim.* [11] **1**, 5 (1934).
[7] H. Gault and J. Burkhard, *C.R. Acad. Sci., Paris* **205**, 1416 (1937).
[8] G. Hesse and K. W. F. Böckmann, *Liebigs Ann.* **563**, 37 (1949).
[9] H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.* **79**, 1488 (1957).

It was thought that the above reaction with glycidaldehyde (II) might have proceeded by initial hydration of the epoxy-group to afford glyceraldehyde (VII), followed by a condensation of the aldol type with acetone. Alternatively, or concurrently, condensation with acetone might have preceeded hydration, with the intermediate formation of the unsaturated epoxy-ketone (VIII). In either case, tautomeric rearrangement of the resulting product (IX) leading to the hydroxy-diketone (X), followed by an intramolecular aldol condensation,[10] could then have yielded the final product (I).



Support for the above mechanism was obtained by carrying out the reaction with glyceraldehyde (VII), which afforded I in similar yield. It seemed that this reaction provided an explanation for the production of I from wood by vigorous treatment with alkali, since alkaline degradation of the cellulose and other carbohydrate constituents could give rise to both acetone[11] and glyceraldehyde.[12]

It has been shown that I is formed not only from wood, but also (in very low yield) from galactose and glucose,* by the action of hot aqueous alkali under pressure.[5] Triose-reductone (XI) was also identified as a product of the galactose reaction, which was therefore explained on the basis of a disproportionation involving two molecules of the hexose:

$$2C_6H_{12}O_6 \rightarrow \underset{\text{I}}{C_6H_8O_2} + \underset{\text{XI}}{2CH(OH):C(OH).CHO} + 4H_2O$$

However, it was found that, while none of the methylcyclopentenolone (I) was obtained by treatment of glucose with aqueous alkali at the reflux temperature, a similar reaction carried out in the presence of acetone produced an easily isolated amount of I.† This confirmed the view that the formation of 3(or 5)-methylcyclopent-2-en-2-ol-1-one (I) by the drastic treatment of carbohydrates with alkali results from a reaction between acetone and glyceraldehyde.

EXPERIMENTAL

3(or 5)-Methylcyclopent-2-en-2-ol-1-one (I)

(a) *From glycidaldehyde.* Glycidaldehyde‡ (20 g) in acetone (40 cc) was added gradually to a stirred mixture of sodium hydroxide (5 g), water (100 cc), and acetone (60 cc); a vigorous exothermic

* In the reaction with glucose, the product (I) was not isolated in the pure state, but was detected by U.V. light absorption studies.

† The failure to isolate I in the absence of acetone could have been due to the small scale of the experiment, or possibly because the conditions were not sufficiently drastic to produce an appreciable amount of acetone *in situ*.

‡ Kindly supplied by Shell Development Company, Emeryville, California.

[10] *Cf.* H. Hunsdiecker, *Ber. Dtsch. Chem. Ges.* **75B**, 455 (1942).
[11] S. Odén and S. Lindberg, *Industr. Engng. Chem.* **19**, 132 (1927).
[12] G. N. Richards and H. H. Sephton, *J. Chem. Soc.* 4492 (1957).

reaction occurred, and the mixture refluxed. Stirring was continued for 2 hr, and then the dark solution was saturated with sodium chloride and washed well with ether. The aqueous layer was acidified with hydrochloric acid and extracted with ether, and the ethereal solution dried ($MgSO_4$) and evaporated. The tarry residue, which had a characteristic smell resembling that of burnt sugar, was extracted several times with boiling light petroleum (b.p. 40–60°); on cooling, the combined extracts deposited needles (0·63 g), m.p. 97–99°. Further purification of the product by sublimation at 90–100°/20 mm, followed by recrystallization from ether–light petroleum (b.p. 40–60°), afforded prisms, m.p. 105–106° (Found: C, 64·2; H, 7·2. Calc. for $C_6H_8O_2$: C, 64·3; H, 7·2%). The infra-red spectrum showed bands at 2·98 (O—H), 5·90 (C=O), and 6·07 μ (C=C). The product reduced Fehling's solution and ammoniacal silver nitrate solution, and gave a violet colour with aqueous alcoholic ferric chloride solution; it was identified as 3(or 5)-methylpent-2-en-2-ol-1-one by a mixed melting-point determination with an authentic specimen, and by comparison of the infra-red spectra.* The bis-phenylhydrazone was obtained as yellow needles (from aqueous ethanol), m.p. and mixed m.p. 140·5–141·5° (Rojahn and Rühl[1] recorded m.p. 138–139°).

Comparative experiments with other alkalis showed that while a similar yield could be obtained with potassium hydroxide in water, the yield was much reduced when potassium hydroxide in methanol was used, and with sodium ethoxide in dry ethanol none of the methylcyclopentenolone could be isolated.

(b) *From glyceraldehyde.* A mixture of glyceraldehyde dimer (5·0 g), acetone (35 cc), sodium hydroxide (1·0 g), and water (40 cc) was refluxed for 5 hr. Working-up as above afforded the crude product (0·11 g), m.p. 100–102°, and recrystallization then gave the methylcyclopentenolone, m.p. and mixed m.p. 105–106°. An equivalent amount of glycidaldehyde (4·0 g), under the same conditions, yielded 0·14 g of the crude product, m.p. 98–100°.

Comparative experiments were also carried out using a higher proportion of alkali and a shorter reaction time. Thus glyceraldehyde (5·0 g), acetone (75 cc), sodium hydroxide (3·0 g), and water (90 cc), refluxed for 5 min, afforded 0·07 g of crude product, m.p. 90–94°; glycidaldehyde (4·0 g) gave 0·06 g of the material, m.p. 93–98°.

(c) *From glucose.* A mixture of glucose (7·5 g), sodium hydroxide (2·0 g), water (45 cc), and acetone (35 cc), refluxed for 2½ hr, yielded 0·09 g of crude product, m.p. 80–84°, raised by recrystallization to 104–105° (undepressed on admixture with an authentic specimen of the methylcyclopentenolone).

A similar experiment was performed in the absence of acetone (using 80 cc of water); none of the methylcyclopentenolone could be isolated by the usual working-up procedure.

Acknowledgement—The author is indebted to Sir Robert Robinson for his interest and advice.

* The identity of the product was kindly suggested by Dr. E. D. Morgan.

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RADIOLYSIS OF LIQUID PROPYLENE: ION–MOLECULE CONDENSATION

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Abstract—Radiolysis of propylene gives mainly hydrogen, and dimeric, trimeric, and other low molecular weight polymeric hydrocarbons.

Detailed analysis of the dimer shows the products to be, in order of concentration, 4-methyl-1-pentene, 1,5-hexadiene, 1-hexene, 2-methylpentane, 2,3-dimethylbutane, 4-methyl-2-pentene, 2-methyl-1-pentene, 2-hexene, and n-hexane.

The relative product concentrations, and the isotope species distribution in the products obtained from radiolysis of a 50:50 mixture of propylene and propylene-d_6, demonstrate that the alkanes, the diene, and much of the olefinic products are formed by combinations of n-propyl, isopropyl, and allyl radicals.

Isotopic species distributions in 4-methyl-1-pentene, 1-hexene, and 2-hexene demonstrate that appreciable fractions of each of these products are formed by a direct condensation of two propylene molecules with intramolecular hydrogen rearrangement. The previously postulated direct dimerization is thus verified, and the idea of its being an ion-molecule condensation receives further support.

INTRODUCTION

THE radiolysis of olefins in liquid phase gives mainly low molecular weight monoolefinic polymers, with some hydrogen and some alkane derived from the alkene.[1] Skeletal structures of the dimers are relatively simple; for example, 1-hexene gave dimeric monoolefins with mainly straight chain and 5-methylundecane skeletons. Lack of C_2 or C_3 branching was believed to indicate only a minor role of allyl-type free radicals. Temperature insensitivity of product distribution required that any entities in thermal equilibrium must not be reacting by paths requiring significant activation energy. Therefore, it was postulated that a new and important reaction in liquid phase is the direct addition of a molecule ion to a molecule, with rearrangement of hydrogen atoms and charge neutralization to give the monoolefinic dimer.

Further conclusions from the C_6 system were difficult to obtain because of complexity of product distribution. A study of propylene radiolysis was undertaken because the number of possible dimeric products is smaller. Hence, essentially complete analysis of the dimer was possible. Furthermore, propylene-d_6 was available, so that experiments could be performed to provide information on the role of the hydrogen atoms.

EXPERIMENTAL

Propylene. Phillips Research Grade propylene was distilled at −78° into a 2 cm o.d. Pyrex irradiation ampule, and sealed *in vacuo*. The sample, weighing 16·7 g, was irradiated by bremsstrahlung in a Dewar at −78° just beneath the slanting gold target[2] of a 3 MeV Van de Graaff, using a 1 mA beam and a 1½ in. linear scan. The dose in the two hour irradiation was determined by ceric ion dosimetry, using identical geometry, to be $3{\cdot}48 \times 10^7$ rads.

[1] P. C. Chang, N. C. Yang and C. D. Wagner, *J. Amer. Chem. Soc.* **81**, 2060 (1959).
[2] C. D. Wagner and V. A. Campanile, *Nucleonics* **17**, [7] 99 (1959).

Volatile products isolated by Toepler pumping at −196° were analyzed mass spectrometrically. Unreacted feed (plus any propane and C_2 material) was collected by distillation at −78° and analyzed similarly. The volatile part of the residue was distilled at 70° into a small tube, sealed, weighed, and later analyzed by gas chromatography. The remaining residue was weighed and analyzed by gas chromatography for presence of C_6 compounds; none was present.

For the gas chromatographic analysis, two different columns were used. With a 40 ft Ucon-filled column at 50°, the spectrum shown in Fig. 1 was obtained. Peaks on this record were identified by a combination of retention-time of known materials and mass spectrometric identification of isolated samples. More accurate quantitative analysis was provided by a 100 m glass capillary column with

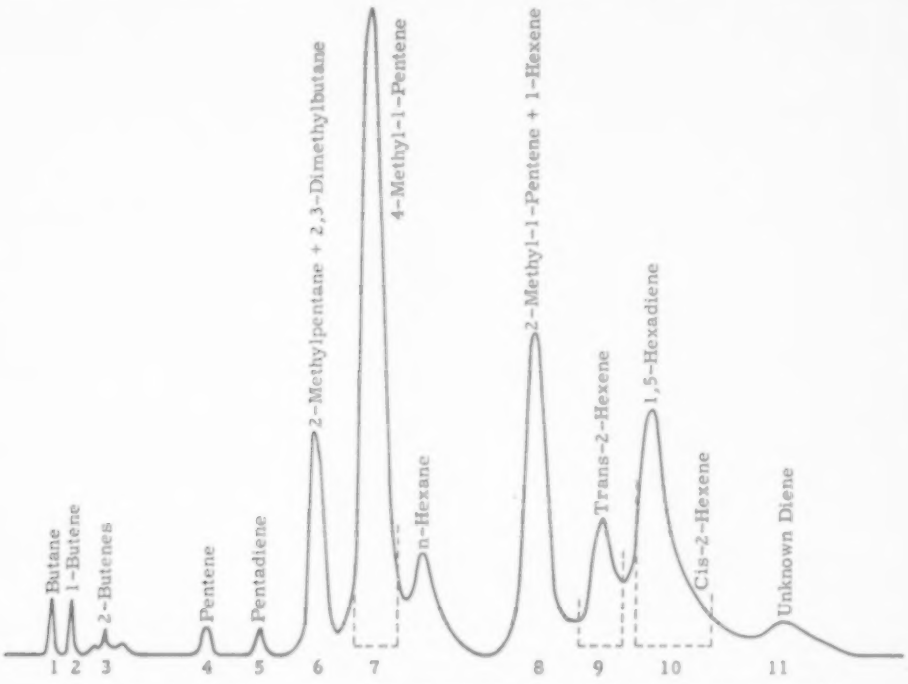

FIG. 1. Analysis and separation of dimer fraction by GLC. 40 ft Ucon-filled column at 50°.

silicone coating, giving the spectrum in Fig. 2. Identification of 2-methylpentane, 1,5-hexadiene, 1-hexene, and *cis*- and *trans*-2-hexene were accomplished by "spiking", and the other identifications were made by anology with the other spectrum.

Propylene plus propylene-d_6. A mixtute of 8·3 mmoles each of Phillips Research Grade propylene and Merck and Co. Ltd. propylene-d_6 was used. The propylene-d_6 contained 3·5% propylene-d_5, corresponding to an overall isotopic purity of 99·4%. The compounds were sealed *in vacuo* in an 8 mm o.d. glass tube equipped with a breakoff seal. The tube was placed in a 10 mm diameter thin-walled titanium tube just beneath the gold target, maintained at −30° to −50° by a stream of cold air passed through the tube, and irradiated for 105 min with bremsstrahlung from the target, which was bombarded with a 1 mA beam at 3 MeV with 2 cm scan. The dose is estimated to be $1{\cdot}4 \times 10^8$ rads.

The products were analyzed as above, except that no effort was made to separate the dimeric and heavier products before the gas chromatographic separation. For this separation the 40 ft Ucon column at 50° was used, with a sample of ca. 50 μl. The spectrum obtained is the same as shown in Fig. 1, and the sample collection periods are shown for those products that were not completely separated.

Determination of isotopic species distribution. The distribution of isotopic species was calculated from the mass spectrum in the parent ion region. First, contributions of ^{13}C to the ion intensities were

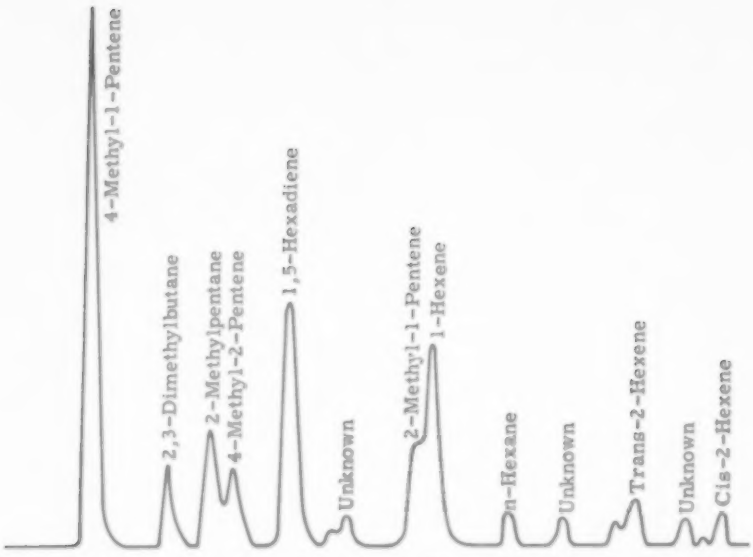

FIG. 2. Analysis of dimer by GLC. 100 m glass capillary column with silicone-filling at 25°.

subtracted. If the compound was known to give negligible fragmentation in the C_6 group (for example, with hexene, ions of $m/q = 72$–83 have negligible intensities compared to that of $m/q = 84$), the ion intensities were taken as those of parent ions and as representative of species distribution. If fragmentation is significant, species analysis was performed by subtracting contributions of parent and fragment ions of successively lighter species, with the assumption that there are no significant isotope effects in fragmentation.

RESULTS

Propylene. Yields of products are shown in Table 1. The *G*-value for conversion of propylene to dimer is 2·16, while the *G* for total converision is ca. 9. Most of the minor unknown products in Table 1 (shown in Fig. 1) have retention times longer than n-hexane, and may be 1,4-hexadiene, 2,3-dimethyl-1-butadiene, and/or *cis*- and *trans*-3-hexene.

Propylene plus propylene-d_6. Mass spectrometric information was obtained on the dimer hydrocarbon cuts obtained by gas chromatography, shown in Fig. 1. Isotopic species distributions that were calculable from mass spectra are given in Table 2. Cut 9 was thought to be a mixture of *trans*-2-hexene and 1,5-hexadiene. In the mass spectrum of this cut the ion intensity ratio for $m/q = 95$ to $m/q = 96$ was 0·41; other ions could not be analyzed as originating with either single component, so that other data obtained on this cut were not meaningful. Cut 10 was mainly 1,5-hexadiene, but the large contribution of hydrogen-poor fragment ions in the C_6 portion of the spectrum made isotopic analysis impossible. Cut 11 was an unknown hexadiene with a large parent ion in the C_6 region.

DISCUSSION

Product analysis for isotopic species in a system composed of equal amounts of two such isotopic species provides useful information on reaction mechanism. For example, if isotope effects are neglected, formation of hexene by simple combination of two propylene molecules with no other molecules or molecular fragments participating

TABLE 1. PRODUCTS OF PROPYLENE RADIOLYSIS

	%*m*	*G*
Hydrogen	0·26	0·6
Methane	0·02	0·04
Propane[a]	0·1	0·2
butane[b]	0·01	0·02
1-Butene[b]	0·012	0·02
2-Butene[b]	0·012	0·02
Pentene[b]	0·008	0·02
Pentadiene[b]	0·008	0·02
2,3-Dimethylbutane	0·032	0·054
2-Methylpentane	0·048	0·080
n-Hexane	0·0133	0·022
4-Methyl-1-pentene	0·227	0·375
4-Methyl-2-pentene[c]	0·033	0·055
2-Methyl-1-pentene	0·02	0·033
1-Hexene	0·085	0·14
trans-2-Hexene	0·018	0·030
cis-2-Hexene	0·0133	0·022
1,5-Hexadiene	0·104	0·17
Others (6)	0·048	0·08

[a] Analytical scheme gave unreliable results for ethylene, but a small amount was clearly present
[b] Values obtained from analysis of Fig. 1.
[c] Identification not certain, based only on retention time of standard.

TABLE 2. ISOTOPIC SPECIES DISTRIBUTION IN PRODUCTS FROM $C_3H_6 + C_3D_6$. MOLE PER CENT SPECIES IN COMPOUND, BY DEUTERIUM ATOMS PER MOLECULE[a]

Cut	Compound	14	13	12	11	10	9	8	7	6	5	4	3	2	1	0
6	2-Methylpentane + 2,3-Dimethylbutane	3·2	11·7	11·3	0·5	3·9	0·6	6·6	20·8	18·9	0·6	1·6	0·3	2·7	8·4	8·9
7	4-Methyl-1-pentene			9·5	8·5	1·2	0·8	1·0	8·0	31·8	8·9	1·3	0·5	1·6	7·1	21·2
8	1-Hexene + 2-methyl-1-Pentene			14·8	10·1	1·4	0·3	0·7	6·8	29·8	10·1	1·0	0·4	1·0	5·8	17·7
11	Hexadiene					12·5	3·6	5·8	2·2	5·5	22·6	9·0	9·3	8·1	4·5	17·1

[a] Analysis assuming no isotope effect in parent ion sensitivity or in fragmentation pattern.

would provide hexene-d_{12}: hexene-d_6: hexene-d_0 in the ratio of 1 : 2 : 1, with no other species. Formation of hexene by combination of C_3H_6, CH_3, and C_2H_3 moieties from different molecules would give species hexene-d_{12}: hexene-d_9: hexene-d_6: hexene-d_3: hexene-d_0 in the ratio 1 : 2 : 2 : 2 : 1. Thus, with no isotope effect, a single mechanism would provide a simple species distribution.

The existence of appreciable isotope effect in most reactions involving deuterium and protium compounds is both a complicating factor and a useful factor. It is a complicating factor in that the quantitative relationship is not the simple statistically-derived one. It is a useful factor in that its magnitude can sometimes provide information on the mechanism.

2-Methylpentane and 2,3-dimethylbutane. Significant parent ion intensities were found for -d_{14}, -d_{13}, -d_{12}, -d_8, -d_7, -d_6, -d_2, -d_1, and -d_0. (The value for -d_{10} is spurious; it is due to pre-emergent hexene-d_{12}.) The mode of formation obviously involves two C_3H_6 entities plus two hydrogen atoms, obtained independently from four molecules.

This would result if the mechanism involves union of two propyl radicals, each derived from C_3H_6 (or C_3D_6) plus H or D (cf. discussion on radical formation below).

Let us assume that these compounds are formed from combinations of propyl and isopropyl radicals present in steady-state concentrations during the irradiation, and determine whether product distribution is consistent with the assumption. With low overall conversion, product distribution reflects initial rates of formation. If we assume all rate constants for combination of these radicals are identical, we can calculate relative steady-state concentrations for each propyl isotopic species: propyl-d_7, propyl-d_6, propyl-d_1, and propyl-d_0 (with no differentiation here between n-propyl and isopropyl).

When this is done from the data for d_{14}, d_{13}, d_{12}, d_8, and d_6, we obtain the following relative steady-state concentrations, normalized to unity:

$$R_7 = 0{\cdot}18$$
$$R_6 = 0{\cdot}34$$
$$R_1 = 0{\cdot}19$$
$$R_0 = 0{\cdot}28$$

and we see the sum $R_7 + R_6$ is close to that of $R_1 + R_0$, indicating nearly equal probabilities of participation by C_3H_6 and C_3D_6 in the formation of propyl. On the other hand, $R_7 = 0{\cdot}54\ R_6$ and $R_1 = 0{\cdot}68\ R_0$. Thus there is a substantial isotope effect favoring H over D for participation in propyl formation. These facts will be used below in a discussion of the mechanism of propyl radical formation.

As a check on the assumption of hexane formation by radical combination, the -d_7, -d_2, -d_1, and -d_0 species destribution calculated from the above relative steady-state radical species concentration is compared with experiment in Table 3.

TABLE 3. BRANCHED HEXANE ISOTOPIC SPECIES DISTRIBUTION

	Found (%)	Calc. (%)
d_7	22·5	23·5
d_2	2·9	3·7
d_1	9·1	10·9
d_0	9·6	8·1

The reasonable agreement between calculated and observed values in Table 3 and the reasonable values for relative steady-state propyl species concentrations provide good evidence that the saturated hydrocarbons are formed by propyl radical combination. It will be shown later that the relative amounts of n-hexane, 2,3-dimethylbutane, and 2-methylpentane among the products are consistent with a particular relative steady-state concentration of n-propyl and isopropyl.

4-*Methyl*-1-*pentene*. This compound is the major volatile product. Important amounts of -d_{11}, -d_7, -d_5, and -d_1 species, in addition to the expected -d_{12}, -d_8, and -d_0, indicate a major mode of formation involves union of C_3H_6, C_3H_5, and H moieties from separate molecules. We may assume the major mechanism involves combination of isopropyl and allyl radicals. However, inspection of the data shows that the

amounts of $-d_{12}$, $-d_6$, and $-d_0$ species appear disproportionately large. Let us assume there are two mechanisms, the radical combination reaction and a "direct" mechanism, the latter giving the excess amounts of the $-d_{12}$, $-d_6$, and $-d_0$ species. The contributions of each may be calculated from the data. To do this, three isotope effects must be considered in the radical combination reaction. These are the probabilities of appearance in the product of C_3D_6 compared to C_3H_6, C_3D_5 compared to C_3H_5, and D compared to H. From the observed ratio $-d_{11}/-d_5$, the first, $(C_3D_6)/(C_3H_6)$, is found to be nearly unity, consistent with the finding on propyl radicals in hexane formation. From the observed ratio $-d_{11}/-d_7$, the second, $(C_3D_5)/(C_3H_5)$ can be expressed in terms of the third, (D)/(H). With the sum of observed mole fractions of $-d_{11}$, $-d_7$, $-d_5$, and $-d_1$

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TABLE 4. SPECIES DISTRIBUTIONS IN 4-METHYL-1-PENTENE

	Obs. (%m)	Radical reaction calc. (%m)	Direct reaction (%m)
$-d_{12}$	10·0	5·3	4·7
$-d_{11}$	8·9	8·8	
$-d_7$	8·4	8·3	
$-d_6$	33·4	19·0	14·4
$-d_5$	9·35	8·8	
$-d_1$	7·45	8·3	
$-d_0$	22·2	13·8	8·5
			27·6

species as a basis, distributions of all species formed by radical combination can then be calculated for any assumed value of (D)/(H). The value of (D)/(H) for propyl radicals in generating the branched hexanes was found to be 0·54–0·68. If 0·6 is used, one obtains the distribution shown in Table 4. For this purpose the small apparent contribution (6 per cent) of other species are ignored. Subtraction of the calculated distribution from the observed distribution gives the excess amounts of $-d_{12}$, $-d_6$, and $-d_0$ species formed by the direct reaction, shown in Table 4. Note that the value for $-d_6$ is reasonable, in the sense that it is close to twice the geometric mean of $-d_0$ and $-d_{12}$. Approximately 28 per cent of the product is formed by the direct reaction. This value is quite insensitive to values assumed for (D)/(H); it varies only from 24 to 31 per cent for values of (D)/(H) between 0·5 and 0·8. Inclusion of the second order correction for the fact that the feed C_3D_6 is 3·5 per cent C_3D_5H has a negligible effect on the results, but accounts for some of the $-d_4$ and $-d_{10}$ species observed.

1-*Hexene* + 2-*Methyl*-1-*pentene*. A similar treatment can be applied to the data on this fraction, yielding the following information;

(1) The fact that $-d_{11}/-d_5$ is unity indicates again that the probability ratio for $(C_3D_6)/(C_3H_6)$ entering into the radical reaction is unity.

(2) The value for (D)/(H) ratio for the radical reaction appears to be in the range 0·5–0·8.

(3) Approximatley 28–32 per cent of the combined product appears to arise from the "direct" reaction. (A major fraction of this may well be the 2-methyl-1-pentene, since the latter is probably not formed by combination of radicals.)

It is concluded the radical reaction to form 1-hexene probably involves the combination of n-propyl and allyl radicals.

1,5-*Hexadiene*. This compound is undoubtedly formed by allyl radical combination. As mentioned above, the isotopic species distribution could not be determined to verify this point.

2-*Hexene*. The ion intensity ratio 95/96 of only 0·41, compared to 0·89 for 4-methyl-1-pentene, demonstrates that a major fraction of the 2-hexene is formed by a direct mechanism.

Unknown hexadiene. The mass spectrum of this compound has low fragment ion intensity in the C_6 region. 2,3-Dimethyl-1,3-butadiene and 2-methyl-1,3-pentadiene, both possibilities on the basis of boiling point, have 81/82 ion intensity ratios of 0·17 and 0·25 respectively.[3] A significant amount of d_9 species ($d_9/d_{10} = 0{\cdot}29$) requires that the reaction be no more than 60 per cent simple recombination of C_3H_5 radicals. Since at least one of the radicals would have to be crotyl or $CH_3—\dot{C}=CH_2$, rather than allyl, it is not surprising that the product is not entirely formed by abstraction of hydrogen from propylene followed by simple radical combination.

ROLE OF FREE RADICALS

The isotopic species distribution for individual compounds has been examined above to obtain information on the mechanism of formation. The relative amounts of the compounds themselves should also furnish some information. If we assume that steady-state concentrations of n-C_3H_7, i-C_3H_7, and C_3H_5 (allyl) radicals exist during the radiolysis, we can determine the consistency of the distribution of the products formed by combination. If we assume for the moment that this is the only mechanism and that the collision efficiencies of the radical combination reactions are equal, we obtain from the relative concentrations of n-hexane, 2,3-dimethyl butane, and 1,5-hexadiene the following relative steady-state concentrations of free radicals: n-propyl, 0·18; isopropyl, 0·29; and allyl, 0·52. Calculation from these gives the amounts of cross-products shown in Table 5. In this table, observed product concentrations are normalized to 100 per cent. The value for 2-methylpentane is not far from the calculated value, and this strengthens the previous conclusion that the alkanes are formed by propyl radical recombination. The calculated values for 4-methyl-1-pentene and 1-hexene are 52 per cent and 87 per cent of those observed, respectively, whereas isotopic species distribution would indicate the contribution by this free

TABLE 5. OBSERVED AND CALCULATED DISTRIBUTIONS OF MAJOR PRODUCTS

	Obs.	Calc
n-Hexane	2·6	
2,3-Dimethylbutane	6·4	
1,5-Hexadiene	20·4	
2-Methylpentane	9·4	8·1
1-Hexene	16·7	14·5
4-Methyl-1-pentene	44·5	23

[3] API Project 44 Mass Spectra.

radical mechanism should be 69–76 per cent for 4-methyl-1-pentene and ca. 85 per cent for 1-hexene.

It is of interest to note that the sum of the n-propyl and isopropyl concentrations is calculated to be almost equal to that of allyl. Two mechanisms of formation of the radicals come to mind that have this stoichiometry and involve no activation energy restrictions:

$$C_3H_6^+ + C_3H_6 \rightarrow C_3H_7^+ + C_3H_5\cdot \quad (1)$$

$$C_3H_7^+ + \epsilon \rightarrow C_3H_7{}^*\cdot$$

$$C_3H_6{}^* \rightarrow C_3H_5\cdot + H \quad (2)$$

$$H + C_3H_6 \rightarrow C_3H_7\cdot$$

Reaction (1) is an ion-molecule reaction first observed by Tal'roze and Lyubimova[4] in a mass spectrometer, and shown by Schissler and Stevenson[5] to have a very high cross-section. The propyl ion, on neutralization, should give propyl radical; ordinarily, isopropyl would be expected to be the favored product, but the necessity for passage through energy-rich periods on reaction and electron recombination might lead one to expect both isomeric radicals. In reaction sequence (2) on the other hand studies have shown that hydrogen atom addition proceeds almost exclusively to the terminal carbon at either 25°[6] or −196°.[7] Formation of n-propyl radicals therefore cannot be accounted for by this path.

It is still necessary to account for the isotope effect in propyl formation. There is an isotope effect in participation of H or D, but not of C_3H_6. Whether the magnitude of the effects can be explained by differences in cross-sections for the ion-molecule reaction in liquid phase is not known.

NATURE OF THE "DIRECT" DIMERIZATION

Regarding direct dimerization we have the following facts:

(1) About 30 per cent of the dimer olefin from propylene is formed by a mechanism involving only the hydrogen atoms of the reacting molecules.

(2) Most of the dimer olefin molecules from 1-hexene[1] have carbon skeletons of n-dodecane or 5-methylundecane.

On the basis of (2), an ion molecule mechanism was proposed,[1] in which an electron-deficient olefin molecule, or molecule-ion, reacts with the double bonded end of a neighboring uncharged molecule. This, followed by intramolecular hydride transfer and electron recombination gives dimer olefin;

$$C_nH_{2n}^+ + C_nH_{2n} \rightarrow [C_{2n}H_{4n}]^+ \xrightarrow[\text{transfer}]{H^-} C_{2n}H_{4n}{}^+ \xrightarrow{\epsilon^-} C_{2n}H_{4n}{}^* \rightarrow C_{2n}H_{4n}$$

The confirmation with labeled propylene of the intramolecular nature of the reaction with respect to hydrogen atoms provides further support for the mechanism.

Indirect evidence for the condensation step includes:

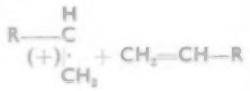
(1) Pottie and Hamill[8] have observed dimeric ions from alkyl iodides with lifetimes greater than a microsecond, by ionization in a mass spectrometer.

[4] V. L. Tal'roze and A. K. Lyubimova, *Dokl. Akad. Nauk SSSR* **86**, 909 (1952).
[5] D. O. Schissler and D. P. Stevenson, *J. Chem. Phys.* **24**, 926 (1956).
[6] W. L. Moore, *J. Chem. Phys.* **16**, 916 (1948).
[7] R. Klein and M. D. Scheer, *J. Phys. Chem.* **62**, 1011 (1958).
[8] R. F. Pottie and W. H. Hamill, *J. Phys. Chem.* **63**, 877 (1959).

(2) Barker[9] with similar techniques observed dimeric ions from benzene, up to $C_{12}H_{11}^+$.

(3) Field, Franklin and Lampe[10] pointed out that heavier ionic products from ion-molecule reactions of ethylene in the mass spectrometer are similar in relative yield to the relative abundances of the same ionic products in the fragmentation of the corresponding C_4 compounds under electron impact in the mass spectrometer. The similarity indicates an unstable dimeric ion was an intermediate in the ion-molecule reaction.

The data on dimeric products of 1-hexene[1] indicate condensation occurs at the double bonded carbons of the two molecules. In that discussion it was pointed out that the excess electron density in the normal olefin molecule is about 0·1 on the terminal double-bonded carbon, with the electron deficiency distributed over the neighboring carbons. On the other hand, in the molecule ion the electron deficiency is shared nearly equally by the two double-bonded carbons. Thus, it may be expected that the attack is the following:



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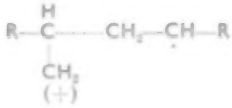
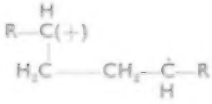
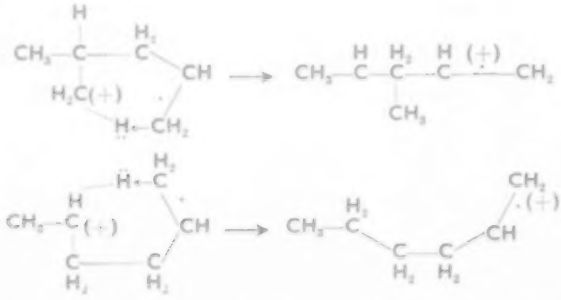


or



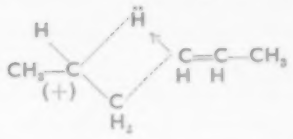
In the case of propylene, hydride transfer in a ring transition state would give the proper product configuration, requiring only charge neutralization and dissipation of the acquired ionization energy to give the major monoolefin products:



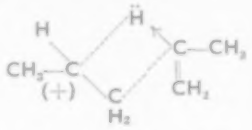
Hydride transfers are common in carbonium ion chemistry and have also been observed in gaseous, unsolvated systems.[11]

[9] R. Barker, *Chem. & Ind.* 233 (1960).
[10] F. H. Field, J. L. Franklin and F. W. Lampe, *J. Amer. Chem. Soc.* **79**, 2665 (1957).
[11] F. H. Field and F. W. Lampe, *J. Amer. Chem. Soc.* **80**, 5587 (1958).

Indications were that 2-hexene was formed from propylene predominantly by this direct mechanism. In this instance a smaller ring or the equivalent would be required:

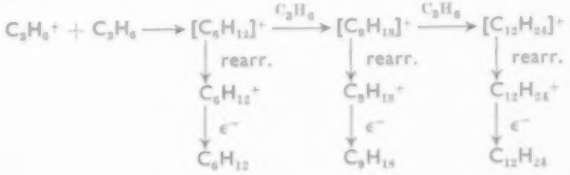


2-Methyl-1-pentene was a minor product. It was isolated only with a much larger amount of 1-hexene. It seems probable it could be formed by the similar direct mechanism, with attack at the central carbon:



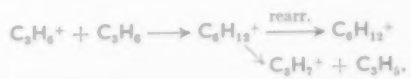
In the condensation step and particularly at the electron recombination step, a problem of energy dissipation exists. The overall sequence from the ion and molecule is exothermic by 10·5 eV, with about 1 eV acquired in the condensation step and 9·5 eV contributed by the ionization energy in the neutralization step. It is believed that fragmentation of these excited species is prevented by the proximity of the neighboring molecules. During the existence of the ion the positive charge induces polarization in the immediately adjacent molecules, and the electrostatic energy of the system is thus diffused over several molecules. Energy transfer can occur not only by vibrational energy transfer in collisions, but also by electrostatic interactions. Thus, as the ion is neutralized, the ionization energy is acquired by the whole cluster as depolarization occurs. Since the energy stored in the surrounding cluster is proportional to r^{-4}, calculation of the contribution by the clustering molecules is extremely sensitive to the value assumed for r. However, for distances of the order of Angstroms, energy storage can be an appreciable fraction of the 9·5 eV.

The proposed mechanism allows possible further polymerization before electron recombination:



Dimerization would thus represent the special case where the chain is terminated by neutralization at that stage.

On first sight it might seem that the formation of propyl ions and allyl radicals should represent an alternative reaction path for the hexene ion complex:



However, the $C_3H_7^+$ is formed very specifically from a propylene ion plus one hydrogen from another molecule, while one should expect such a decomposition to provide at

least some further mixing of hydrogens. That specific atom transfers can occur without mixing in ion-molecule reactions where product ions are of weight intermediate between primary and dimer ion is shown in the reaction $CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$.[12] Therefore, it is believed that these reactions result from a dimeric ion complex of higher energy and shorter life-time, a complex formed from a propylene ion possessing excess vibrational energy acquired in the primary ionization act.

A mechanism alternative to the ion-molecule condensation, yet consistent with intramolecular role of the hydrogen, is the concept that propyl and allyl radicals formed in this way recombine before they leave the reaction cage. This mechanism cannot explain the specificity of carbon skeletons in the dimer from 1-hexene, nor can it be extended to account for the higher molecular weight polymers.

Another possible mechanism is similar to that invoked by Dole, Milner and Williams,[13] involving reaction of double-bonded carbons in an activated state with a neighboring saturated chain. Such a mechanism applied to these olefinic systems would have to represent a special case of attack at the double bond, rather than an alkyl chain. A mechanism involving excited molecules cannot be rejected, but on the other hand, there is no supporting evidence for its occurrence in this system.

This system with propylene in a sense represents a special case of olefin radiolysis, for propylene is a small molecule and its derivative, the allyl radical, is symmetrical. The fact that the fraction of monoolefin in the dimer is only 0·64, compared to ca. 0·9 with 1-hexene, indicates that the direct dimerization is more important with larger olefins. The greater number of modes of energy dissipation in large molecules may be responsible for the difference. A central feature of the ion-molecule mechanism for condensation is the necessity that close neighboring molecules participate in electrostatic and collisional energy transfer. For this reason these condensations are probably peculiar to liquid or solid phase.

CONCLUSIONS

(1) An important amount of dimeric product is formed by a direct condensation of two olefin molecules, believed to proceed as an ion-molecule condensation, followed by hydrogen atom rearrangement and charge neutralization.

(2) With propylene the saturated hexanes (2,3-dimethylbutane, 2-methylpentane, and n-hexane) are formed by combination of n-propyl and isopropyl radicals. Much of the olefinic dimer not formed by direct ion-molecule condensation is formed by combination of allyl with propyl or isopropyl radicals.

(3) Formation of propyl radicals involves addition of atoms of hydrogen to propylene, by a mechanism that gives a significant fraction (38 per cent) of n-propyl. This lack of specificity is evidence against addition of thermal hydrogen atoms to propylene, so an ion-molecule mechanism is proposed.

Acknowledgements—The author gratefully acknowledges helpful discussions with Drs. G. M. Coppinger and D. P. Stevenson.

[12] C. D. Wagner, P. A. Wadsworth and D. P. Stevenson, *J. Chem. Phys.* **28**, 517 (1958).
[13] Malcolm Dole, D. C. Milner and T. F. Williams, *J. Amer. Chem. Soc.* **80**, 1580 (1956).

Tetrahedron, 1961, Vol. 14, pp. 175 to 189. Pergamon Press Ltd. Printed in Northern Ireland

NEW TYPES OF THE *TRANS*-GLYCOSYLATION REACTION

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(*Received* 31 *October* 1960)

Abstract—Newer types of *trans*-glycosylation of N-arylglycosylamines have been realised in which N-arylglycosylamines and monosaccharides as well as two N-arylglycosylamines with different amine and sugar components took place. Results are summarized in Tables 1–4. *Trans*-glycosylation of acetylated N-arylglycosylamine with monosaccharide means a new method for the preparation of partly acetylated monosaccharides. Mechanisms of the reactions have been discussed.

IT was reported previously[1] that the scope of the *trans*-glycosylation reaction of N-arylglycosylamines may be extended, so that not only the arylamine, but also the glycosyl and acetylated glycosyl part of the molecule may be exchanged. We have now found that *trans*-glycosylations may be realised in almost any variation.

In previous papers[2] and in examples known until now, the following types of *trans*-glycosylation were described:

Type Ia

The N-arylglycosylamine is acted upon by another arylamine, forming the glycosylamine of the new arylamine and liberating the amine from the original arylglycosylamine.

$$\text{glycosyl-NH-aryl} + \text{H}_2\text{N-aryl'} \rightleftharpoons \text{glycosyl-NH-aryl'} + \text{H}_2\text{N-aryl}$$

Type Ib

Reaction of an N-arylglycosylamine acetate with an aromatic amine results in the combination of the O-acetylglycosyl part with the other amine forming a new N-arylglycosylamine acetate.

$$(\text{Ac})_n\text{-glycosyl-NH-aryl} + \text{H}_2\text{N-aryl'} \rightleftharpoons (\text{Ac})_n\text{-glycosyl-NH-aryl'} + \text{H}_2\text{N-aryl}$$

Trans-glycosylations of types Ia and Ib were carried out in alcoholic solutions, in the presence of acid catalysts. The conversions were shown to be equilibrium reactions, and could be made reversible under suitable conditions. The reactions were comparatively rapid in solutions of a molarity of 0·2–0·5; the product, as a component of the equilibrium system, separated from the mixture in crystalline form in good yield. When suitable solvents and concentrations are used the method may be applied for preparative purposes.

[1] R. Bognár and P. Nánási, *Acta Chim. Hung.* **12**, 115 (1957); unpublished results communicated at I.U.P.A.C. Congress, Paris 1957.
[2] R. Bognár and P. Nánási, *Nature, Lond.* **171**, 475 (1953); *J. Chem. Soc.* 189 (1955); *Magyar Kémiai Folyóirat* **62**, 88 (1956); R. Bognár, P. Nánási and E. Nemes-Nánási, *J. Chem. Soc.* 193 (1955); *Magyar Kémiai Folyóirat* **62**, 271 (1956).

In addition, it was shown that the reaction was true *trans*-glycosylation and not hydrolysis followed by reglycosylation. This was also true for more dilute solutions (0·04 M concentration), and when about 10 per cent water was present. (*J. Chem. Soc.* In press.)

We now report the feasibility of achieving the *trans*-glycosylation reaction in cases described below.

Type IIa

Reaction of N-arylglycosylamine with a monosaccharide leads to the formation of an N-arylglycosylamine containing the new sugar, and the original sugar moiety is released. The possibility of this type of reaction was demonstrated independently by Inoue *et al.*[3], by the technique of paper chromatography.

glycosyl-NH-aryl + glycosyl'-OH ⇄ glycosyl'-NH-aryl + glycosyl-OH

Respective experiments and their results are summarized in Table 1.

This type of *trans*-glycosylation gives best yields and the purest products in the presence of a small amount of water (5–10 per cent). In absolute alcohol prolonged refluxing is necessary for dissolving the starting materials, when the solutions become strongly coloured. Free sugars have, in general, very low solubilities in anhydrous alcohol. A fair yield is obtained if the solvent contains a small amount of water or pyridine. When the reaction is carried out in aqueous medium, the possibility of hydrolysis and subsequent reglycosylation must be taken into consideration. True *trans*-glycosylation and glycoside formation after previous hydrolysis may, in our opinion, take place as parallel reactions.

When either component is taken in 1 mole excess, yields of the crude product are increased; however, the purity of the product is not satisfactory, therefore no appreciable gain is found from the preparative point of view by employing 1 mole excess of one of the components.

Yield percentages given in the Table 1 for the crude product relate to materials containing less than 10 per cent impurity. In general they are about 95 per cent pure.

Type IIb

Reaction of an N-arylglycosylamine acetate with a free simple sugar, gives a new N-arylglycosylamine and a monosaccharide acetate with a free hydroxyl group on $C_{(1)}$

$(Ac)_n$-glycosyl-NH-aryl + glycosyl'-OH ⇄ glycosyl'-NH-aryl + $(Ac)_n$-glycosyl-OH

Experiments and results are shown in Table 2.

Aqueous alcohol was employed as the solvent, because in this type of reaction one component is again a free sugar. Ammonium chloride was found to be a better catalyst than hydrochloric acid, but best yields were obtained in the presence of pyridine with hydrochloric acid catalyst.

As the result of the reaction, the new, non-acetylated, free N-arylglycosylamine

[3] Y. Inoue, K. Onodera and S. Kitaoka, *J. Agric. Chem. Soc. Japan* **27**, 5 (1953).

TABLE 1

Experiment		Reactants (Mole ratio of the reactants = 1:1 except given cases)	Solvent	Catalyst	Period of boiling	Product	Yield (%)	
Type	No						Crude	Pure
IIa	1	N-*p*-tolyl-D-glucosylamine + D-mannose	94% EtOH	HCl	5	N-*p*-tolyl-D-mannosylamine	76·5	70
IIa	2	N-*p*-tolyl-D-glucosylamine + D-mannose	94% EtOH	HCl	1	N-*p*-tolyl-D-mannosylamine	63·5	56
IIa	3	N-*p*-tolyl-D-glucosylamine + D-mannose	75% MetOH	HCl	5	N-*p*-tolyl-D-mannosylamine	55	53·8
IIa	4	N-*p*-tolyl-D-glucosylamine + D-mannose	94% EtOH + Py	HCl	5	N-*p*-tolyl-D-mannosylamine	56·5	
IIa	5	N-*p*-tolyl-D-glucosylamine + D-mannose	94% EtOH + Py	HCl	5	N-*p*-tolyl-D-mannosylamine	73·2	69
IIa	6	N-*p*-tolyl-D-glucosylamine + D-mannose	94% EtOH	NH_4Cl	5	N-*p*-tolyl-D-mannosylamine	63	60
IIa	7	N-*p*-tolyl-D-glucosylamine + D-mannose	abs. EtOH	HCl	8	N-*p*-tolyl-D-mannosylamine	6·7	6·1
IIa	8	N-*p*-tolyl-D-glucosylamine + D-mannose	abs. EtOH + Py	HCl	15	N-*p*-tolyl-D-mannosylamine	67	64·5
IIa	9	N-*p*-tolyl-D-glucosylamine + D-mannose	abs. EtOH	NH_4Cl	5	N-*p*-tolyl-D-mannosylamine	33·3	32
IIa	10	N-*p*-tolyl-D-glucosylamine + D-mannose	abs. EtOH	—	5	N-*p*-tolyl-D-mannosylamine	20	17
IIa	11	N-*p*-tolyl-D-glucosylamine + D-mannose	abs. EtOH	—	120, 40°	N-*p*-tolyl-D-mannosylamine	35	
IIa	12	N-*p*-tolyl-D-glucosylamine + D-mannose	94·6% EtOH + Py	—	5 after 2 days		0 20	17
IIa	13	N-*p*-tolyl-D-glucosylamine + D-mannose	94·6% EtOH	—	5 after 2 days	N-*p*-tolyl-D-mannosylamine	7 40	
IIa	14	N-*p*-tolyl-D-glucosylamine + D-mannose 1:2	94% EtOH	HCl	5	N-*p*-tolyl-D-mannosylamine	93·5	75
IIa	15	N-*p*-tolyl-D-glucosylamine + D-mannose 1:2	75% EtOH	HCl	5	N-*p*-tolyl-D-mannosylamine	73	61·6
IIa	16	N-*p*-tolyl-D-glucosylamine + D-mannose 1:0·5	94% EtOH	HCl	5	N-*p*-tolyl-D-mannosylamine	80	72·2
IIa	17	N-*p*-tolyl-D-glucosylamine + D-mannose 1:2	94% EtOH + Py	HCl	5	N-*p*-tolyl-D-mannosylamine	80	62·7
IIa	18	N-*p*-tolyl-D-glucosylamine + D-mannose 1:2	94% EtOH	NH_4Cl	5	N-*p*-tolyl-D-mannosylamine	76·6	64·1
IIa	19	N-*p*-tolyl-D-glucosylamine + D-mannose 1:0·5	94% EtOH	NH_4Cl	5	N-*p*-tolyl-D-mannosylamine	80	73·6
IIa	20	N-*p*-tolyl-D-galactosylamine + D-mannose	abs. EtOH	HCl	30	N-*p*-tolyl-D-mannosylamine	27·5	
IIa	21	N-*p*-tolyl-D-galactosylamine + D-mannose	abs. EtOH	HCl	5	N-*p*-tolyl-D-mannosylamine	70	66·2
IIa	22	N-*p*-tolyl-D-glucosylamine + D-galactose	97% EtOH	HCl	10	N-*p*-tolyl-D-galactosylamine	65	
IIa	23	N-*p*-tolyl-D-glucosylamine + D-galactose	97% EtOH + Py	HCl	5	N-*p*-tolyl-D-galactosylamine	72·5	
IIa	24	N-*p*-tolyl-D-glucosylamine + D-galactose	abs. EtOH	HCl	40	N-*p*-tolyl-D-galactosylamine	25 and 28	
IIa	25	N-*p*-Br-phenyl-D-glucosylamine + D-galactose	90% MeOH + Py	HCl	5	N-*p*-Br-phenyl-D-galactosylamine	67·5	
IIa	26	N-*p*-Br-phenyl-D-glucosylamine + D-galactose 1:2	90% MeOH + Py	HCl	5	N-*p*-Br-phenyl-D-galactosylamine	77·5	
IIa	27	N-*p*-Br-phenyl-D-glucosylamine + D-galactose 1:1	90% EtOH	NH_4Cl	15	N-*p*-Br-phenyl-D-galactosylamine	21·5	
IIa	28	N-*p*-Br-phenyl-D-glucosylamine + D-galactose	90% EtOH	NH_4Cl	15	N-*p*-Br-phenyl-D-galactosylamine	29·5	
IIa	29	N-*p*-NO_2-phenyl-D-glucosylamine + D-galactose	90% EtOH	HCl	15	N-*p*-NO_2-phenyl-D-glucosylamine	35·5	15
IIa	30	N-*p*-NO_2-phenyl-D-glucosylamine + D-galactose	90% EtOH + Py	HCl	15	N-*p*-NO_2-phenyl-D-glucosylamine	50	34

TABLE 2

Experiment Type	Experiment No	Reactants (Mole ratio of the reactants = 1:1 except given cases)	Solvent	Catalyst	Period of boiling (min)	Product	Yield (%)
IIb	1	N-*p*-tolyl-D-glucosylamine tetraacetate + D-mannose	96% EtOH	HCl + Py	15	N-*p*-tolyl-D-mannosylamine	78
IIb	2	N-*p*-tolyl-D-glucosylamine tetraacetate + D-mannose	96% EtOH	NH_4Cl	30	N-*p*-tolyl-D-mannosylamine	64·5
IIb	3	N-*p*-tolyl-D-glucosylamine tetraacetate + D-mannose	96% EtOH	HCl + Py	10	N-*p*-tolyl-D-mannosylamine + D-glucosetetracetate	75 61
IIb	4	N-*p*-tolyl-D-glucosylamine tetraacetate + D-mannose	96% EtOH	HCl	10	0	0
IIb	5	N-*p*-tolyl-D-glucosylamine tetraacetate + D-mannose	96% EtOH	—	10	0	0
IIb	6	N^1-*p*-sulphamylphenyl-D-glucosylamine tetraacetate + D-glucose	abs. EtOH	HCl + Py	15	N^1-*p*-sulphamylphenyl-D-glucosylamine	17
IIb	7	N-*p*-tolyl-D-mannosylamine-tetraacetate + D-mannose	96% EtOH	HCl + Py	10	N-*p*-tolyl-D-mannosylamine + D-mannosetetraacetate	63·5 54·5
IIb	8	N-*p*-tolyl-D-galactosylamine-tetraacetate + D-mannose	96% EtOH	HCl + Py	10	N-*p*-tolyl-D-mannosylamine + D-galactose-tetraacetate	64·5 46·8

TABLE 3

Experiment Type	Experiment No	Reactants (Mole ratio of the reactants = 1:1 except given cases)	Solvent	Catalyst	Period of boiling (min)	Product	Yield (%)
IIIa	1	N-*p*-nitrophenyl-D-glucosylamine + N-*p*-tolyl-D-galactosylamine	abs. ethanol	HCl	10	N-*p*-nitrophenyl-D-galactosylamine	42
IIIa	2	N-*p*-nitrophenyl-D-glucosylamine + N-*p*-tolyl-D-galactosylamine	abs. ethanol	HCl + Py	5	N-*p*-nitrophenyl-D-galactosylamine	42
IIIa	3	2 moles N-*p*-nitrophenyl-D-glucosylamine + N-*p*-tolyl-D-galactosylamine	abs. ethanol	HCl	4	N-*p*-nitrophenyl-D-galactosylamine	55
IIIa	4	2 moles N-*p*-nitrophenyl-D-glucosylamine + N-*p*-tolyl-D-galactosylamine	abs. ethanol	—	10	N-*p*-nitrophenyl-D-galactosylamine	0
IIIa	5	N^4-*p*-sulphamylphenyl-D-galactosylamine + N-*p*-tolyl-D-glucosylamine	abs. methanol	HCl	5	N^1-*p*-sulphamylphenyl-D-glucosylamine	15·5
IIIa	6	N^4-*p*-sulphamylphenyl-D-galactosylamine + N-*p*-tolyl-D-glucosylamine	abs. methanol	HCl + Py	5	N^1-*p*-sulphamylphenyl-D-glucosylamine	24
IIIa	7	0·5 mole N^4-*p*-sulphamylphenyl-D-galactosylamine + N-*p*-tolyl-D-glucosylamine	abs. methanol	HCl + Py	5	N^1-*p*-sulphamylphenyl-D-glucosylamine	27·5
IIIa	8	2 moles N^1-*p*-sulphamylphenyl-D-galactosylamine + N-*p*-tolyl-D-glucosylamine	abs. methanol	HCl + Py	5	0	—
IIIa	9	N^4-*p*-sulphamylphenyl-D-galactosylamine + N-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine	abs. methanol	NH_4Cl	30	N^1-*p*-sulphamylphenyl-D-glucosylamine	18·2
IIIa	10	N^4-*p*-sulphamylphenyl-D-galactosylamine + N-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine	abs. methanol	HCl + Py	5	N^1-*p*-sulphamylphenyl-D-glucosylamine	20

separates from the reaction mixture, and the 2,3,4,6-tetra-O-acetyl-hexoses could readily be isolated from the solution. This is a new method for preparing, e.g. partly acetylated monosaccharides. Though yields are only around 40–50 per cent, this new method appears to be simpler than the classic synthesis.

A preparative method for the *trans*-glycosylation of N-arylglycosylamines by means of partly acetylated sugars has not yet been realized.

Type IIIa

When two different N-arylglycosylamines having different sugar and amine parts react with one another, total or double *trans*-glycosylation can occur. In this case, both possible new N-arylglycosylamines are obtained.

glycosyl-NH-aryl + glycosyl'-NH-aryl' $\rightleftarrows$ glycosyl-NH-aryl' + glycosyl'-NH-aryl

Experiments and results are summarized in Table 3.

These reactions were carried out in anhydrous methanol or ethanol using absolutely dry reagents. Hydrogen chloride in the presence of pyridine proved to be the best catalyst; no *trans*-glycosylation occured in the absence of an acid catalyst. Only one of the two possible new N-arylglycosylamines have been isolated so far in crystalline form from the equilibrium reaction mixture, under conditions depending upon the solubilities, with special regard to the nature and quantity of the solvent.

Type IIIb

A variation of double *trans*-glycosylation, when an N-arylglycosylamine acetylated in its sugar moiety is acted upon by a free, non-acetylated N-arylglycosylamine, may be regarded as a new class of *trans*-glycosylation. In this case, the acetyl–glycosyl part becomes attached to the other amine.

$(Ac)_n$-glycosyl-NH-aryl + glycosyl-NH-aryl' $\rightleftarrows$ $(Ac)_n$-glycosyl-NH-aryl' + glycosyl-NH-aryl

Only one example of this reaction has been realized so far, however, in an excellent yield. Data are given in Table 4.

It appears that this type of reaction also gives best results, and is carried out most readily in the presence of hydrogen chloride and pyridine, and in anhydrous solvents.

The above experimental results lead to the conclusion that N-arylglycosylamines or their acetates form an equilibrium system with the other amine, sugar, or new N-arylglycosylamine present; this reaction which takes place under the action of proton-catalysis in alcoholic solution, is comparatively rapid. The resulting mixture contains the possible new N-arylglycosylamine, which may separate from the reaction mixture as a consequence of its slight solubility, and may thus shift the equilibrium of the reaction, and can under proper conditions be obtained in crystalline form, in yields often useful for preparative purposes. It is assumed that the reactions should be regarded

TABLE 4

Experiment		Reactants (Mole ratio of the reactants = 1:1 except given cases	Solvent	Catalyst	Period of boiling (min)	Product	Yield (%)
Type	No						
IIIb	1	N^1-*p*-sulphamylphenyl-D-glucosylamine tetraacetate + N-*p*-tolyl-D-glucosylamine. 2 moles.	96% ethanol	HCl	15	N^4-*p*-sulphamylphenyl-D-glucosylamine	90

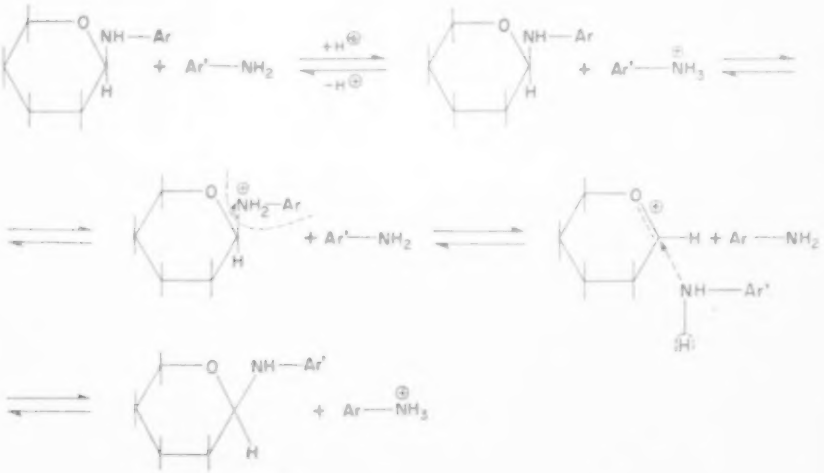
as true *trans*-glycosylations in all cases when the reactions were carried out in anhydrous medium (types IIIa and IIIb), by analogy with the proved real *trans*-glycosylations of types Ia and Ib (*J. Chem. Soc.* In press). When the reactions were carried out in the presence of water a small amount of which improves the yields, and is necessary for dissolving the sugar, hydrolysis and subsequent reglycosylation must also be taken into consideration. (Types IIa and IIb.)

In our opinion, *trans*-glycosylation reactions as special cases of *trans*-acetalization are comparable with proton-catalysed *trans*-esterification reactions, in which latter type an acyl–oxygen bond is split, (*cf.*[4]), and the formation of a transient acylium ion is assumed. Formation of a transient glycosylium ion or to be more exact the

mesomerie cyclic cation may be considered in the cases of *trans*-glycosylations, which offers a satisfactory explanation for the mechanism of the individual types of *trans*-glycosylations, as suggested in our previous papers. The *trans*-glycosylation mechanism presented by Isbell and Frush[5], involving an intermediate imonium ion /R—$\overset{\oplus}{C}$=NH—R'/ and transient complexes derived therefrom, could be applied to *trans*-glycosylations of types IIIa and IIIb only with difficulty; this mechanism, together with the possibility of the formation of the acyclic oxonium cation (R—CH=$\overset{\oplus}{O}$H) should be taken into account in the case of *trans*-glycosylations of types IIa and IIb.

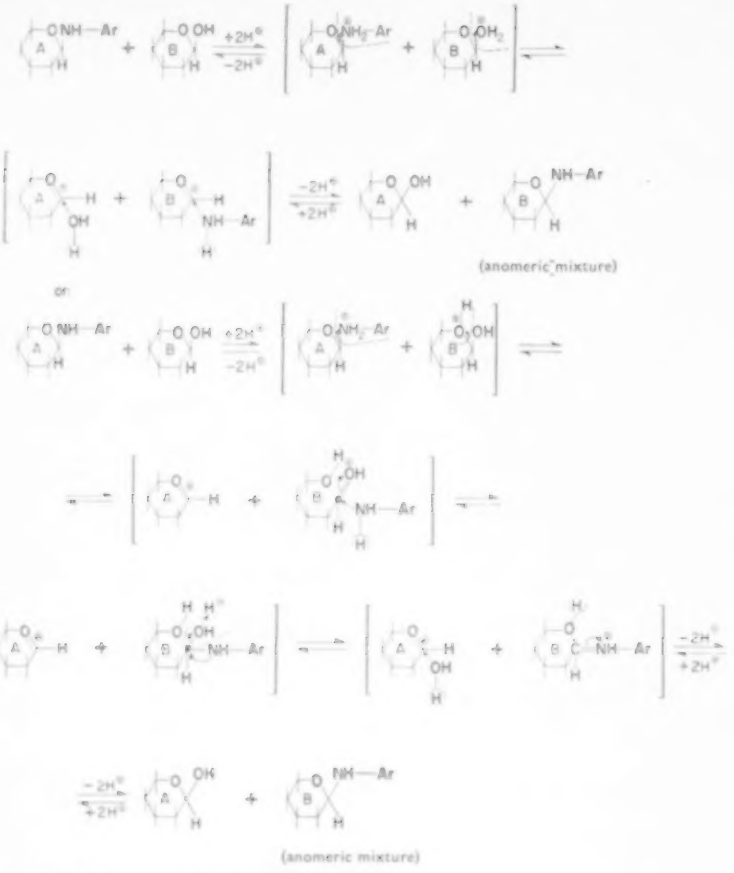
Suggested mechanisms

(1) Trans-*glycosylations of types* Ia *and* Ib.

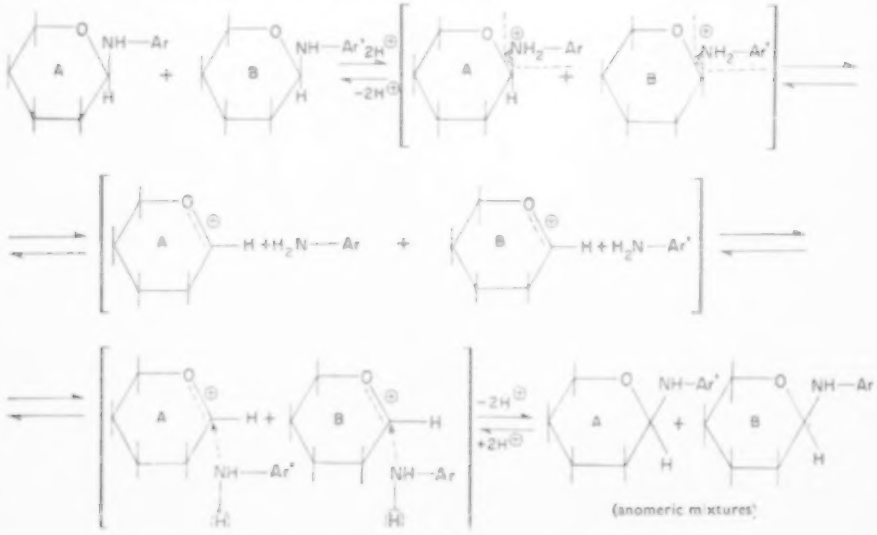


[4] C. H. Ingold, *Structure and Mechanism* p. 767. G. Bell, London (1953).
[5] H. S. Isbell and H. L. Frush, *J. Org. Chem.* **23**, 1309 (1958).

(2) Trans-*glycosylations of types* IIa *and* IIb.



(3) Trans-*glycosylations of types* IIIa *and* IIIb.



Further work is in progress to extend the scope of *trans*-glycosylation reactions, and to investigate the reaction mechanism.

EXPERIMENTAL

Melting points are uncorrected. Mixed melting points were determined with materials of standard purity. Optical activities were always measured in pyridine.

Trans-*glycosylation Reactions belonging to Type* IIa

Trans-glycosylation of N-arylglycosylamines and free sugars.

N-p-*Tolyl*-D-*mannosylamine by* trans-*glycosylation from* N-p-*tolyl*-D-*glucosylamine and* D-*mannose*

(IIa; 1). N-*p*-Tolyl-D-glucosylamine (3·0 g, 1 mole) m.p. 112–113°; $[\alpha]_D = -96°$ and D-mannose (2·2 g, 1 mole) were dissolved in 96% ethanol (30 ml) containing hydrochloric acid (0·5 ml). Dissolution of the starting materials took place in about 1 1/2 min, and the reaction solution was refluxed for 5 min. The mixture was allowed to stand at room temperature, when deposition of a crystalline precipitate shortly occurred. Next day, the crude product was filtered (2·15 g), m.p. 175° (decomp.), $[\alpha]_D^{20} = -162°$ (*c*, 1). The mother liquor gave another crop (0·15 g) on the next day. Yield of total crude product was 76·5%.

The purity of the N-*p*-tolyl-D-mannosylamine crude product was checked by paper chromatography in several experiments (for a description of the technique, *cf. J. Chem. Soc.* In press). In general, a purity of about 94–95% was found, the product containing about 2–3% of N-*p*-tolyl-D-glucosylamine and 2–3% of mannose.

The crude product (1·0 g) was recrystallized from 75% aqueous methanol to give 0·72 g of m.p. 183° $[\alpha]_D^{21} = -179°$ (*c*, 1). (Found: N, 5·2%).

The crude product can very readily be purified by the following method which was applied also in the other experiments: The material (1·5 g) was thoroughly digested at room temperature with 75% aqueous methanol (20 ml), and filtered by suction. This purification, accompanied by a loss of 8%, gave a product (1·28 g), $[\alpha]_D^{22} = -178°$ (*c*, 1), m.p. 184° (decomp.), undepressed after admixture with pure N-*p*-tolyl-D-mannosylamine, m.p. 183–184°;[6] 184°; $[\alpha]_D^{20} = -181°$.[8] (Found: C, 57·0; H, 7·05; N, 5·17. Calc. for $C_{13}H_{19}O_5N$ (269·2) C, 58·0; H, 7·1; N, 5·2%).

Other experiments (preparation, purification and checking of purity), in connexion with the *trans*-glycosylation of N-*p*-tolyl-D-glucosylamine and D-mannose, were carried out in the manner described above, with some modifications concerning the solvent, catalyst, ratio of reagents or time of refluxing, as described below.

(IIa, 2). This was done as in "IIa, 1" except that the reaction mixture was boiled for 60 min. After standing for 1 day, a precipitate (1·4 g) was obtained, m.p. 174°, $[\alpha]_D^{21} = -168°$. After the mother liquor had been stored for 5 days additional product (0·4 g, total yield 63·5%), m.p. 177° (decomp.) was obtained.

(IIa, 3). This was the same as "IIa, 1," except that a solvent mixture of methanol (30 ml) and water (7 ml) was employed instead of ethanol. The first crop (1·3 g) obtained after 1 day had m.p. 176° (decomp.), $(\alpha)_D^{22} = -171°$ (*c*, 0·6). This with the second crop (0·35 g collected 1 day later) gave a yield of 55%. Purification with cold aqueous methanol resulted in 2% loss, and gave a completely pure product, m.p. 184° (decomp.), $[\alpha]_D^{21} = -177°$ (*c*, 1). (Found: C, 57·6; H, 6·9; N, 5·17%).

(IIa, 4). As experiment "IIa, 1," but pyridine (3 ml) was added. The crude product precipitated after 2 days (1·7 g, 56·5%), had m.p. 170° (decomp.).

(IIa, 5). As experiments "IIa, 1" and "IIa, 4," but in the presence of less pyridine (1 ml). Crude product (2·2 g; 73·2%) had m.p. 170° (decomp.). Yield of the pure compound was 69%.

(IIa, 6). As experiment "IIa, 1," but in the presence of less ethanol (20 ml), and with ammonium chloride (0·2 g) catalyst. The crude product (1·9 g; 63%) had m.p. 174° (decomp). Washing with aqueous methanol gave 60% m.p. 184°, $[\alpha]_D^{21} = -179°$ (*c*, 1).

(IIa, 7). As experiment "IIa, 1," but under absolutely anhydrous conditions, in ethanol (20 ml) containing dry hydrogen (0·035 g). Time of reflux: 8 min. The reaction mixture was quite dark.

[8] G. P. Ellis and J. Honeyman: *J. Chem. Soc.* 1496 (1952); F. Weygand, *Ber. Dtsch. Chem. Ges.* **72**, 1667 (1939).

Total precipitation under cooling in ice 0·2 g (6·7%), m.p. 170° (decomp.); $[\alpha]_D^{20} = -166°$ (*c*, 1). Yield after washing with aqueous methanol 6·1%, m.p. 184° (decomp.), $[\alpha]_D^{20} = -176°$ (*c*, 1). (Found: N, 5·12%).

(IIa, 8). The experiment was the same as "IIa, 7," but pyridine (0·5 ml) was added. The mixture did not turn so dark as in experiment "IIa, 7." The product (2·02 g, 67%), precipitated directly, was of high purity, m.p. 183°; $[\alpha]_D = -168°$ (*c*, 1). Yield of purified product 64·5%. (Found: N, 5·15%).

(IIa, 9). As "IIa, 1," but the experiment was carried out in anhydrous alcohol (20 ml), and ammonium chloride (0·2 g) was used instead of hydrochloric acid catalyst, with a reflux time of 15 min. The crude product (1·0 g, 33·3%) had m.p. 172° (decomp.). Washing with aqueous methanol gave a product (32%) of m.p. 183° (decomp.), $[\alpha]_D^{20} = -177°$ (*c*, 1). (Found: N, 5·22%).

(IIa, 10). The experiment was carried out as "IIa, 1," but in anhydrous ethanol (20 ml) and without a catalyst. Complete dissolution required 50 min. The material (0·5 g), collected at room temperature on the second day, had m.p. 160° (decomp.). Purification of the crude product (20% yield) with aqueous methanol resulted in 15% loss, giving a substance decomposing at 184°.

(IIa, 11). The experiment was the same as "IIa, 10," but the mixture was heated only to 40°. Complete dissolution required shaking for 2 hr. The crude product (1·05 g, 35%) had m.p. 163° (decomp.), $[\alpha]_D^{21} = -165°$ (*c*, 1). (Found: N, 5·15%).

(IIa, 12). As experiment "IIa, 1," but without hydrochloric acid catalyst, and in the presence of pyridine (3 ml). The crude product (0·6 g, 20%) separated after 2 days, m.p. 170° (decomp.).

(IIa, 13). As experiment "IIa, 12," but in the absence of pyridine. Standing for 1 day gave a small amount of precipitate [0·2 g, m.p. 170° (decomp.)]. Additional 2 days resulted in a second crop (1·0 g), m.p. 170° (decomp.), $[\alpha]_D^{20} = -163°$ (*c*, 1). (Found: N, 5·07%). Yield of crude product was 40%.

(IIa, 14). As experiment "IIa, 1," but with a double amount of mannose (4·4 g, 2 moles). A rich crystalline precipitate (2·3 g, m.p. 175° with decomp.) was obtained on cooling, an additional crop (0·55 g, m.p. 162°, decomp.) being obtained on the second day at room temperature. An analysis by paper chromatography showed the product to contain free mannose (10–12%) and *p*-tolyl-D-glucosylamine (8–10%). The crude product (yield 93·5%) was purified by means of 75% aqueous methanol with a loss of 20%, to give very pure *p*-tolyl-D-mannosylamine, homogenous also according to control by paper chromatography; m.p. 184° $[\alpha]_D^{21} = -179°$ (*c*, 1·2). (Found: N, 5·09%).

(IIa, 15). The experiment was the same as "IIa, 14," but water (7 ml) was added. The material collected after 2 days was 2·1 g, m.p. 178° (decomp.), $[\alpha]_D^{20} = -168°$ (*c*, 1). A small amount was obtained the next day (0·1 g), of m.p. 165° (decomp.). Yield of crude product (calculated on basis of *p*-tolyl-D-glucosylamine used) was 73%. Yield of purified product was 61·6%.

(IIa, 16). As experiment "IIa, 1," but only half of the amount of mannose (1·1 g, 0·5 mole) was used. Standing for 2 days resulted 1·2 g product (80%, based on mannose), m.p. 173–174° (decomp.), $[\alpha]_D^{20} = -160°$ (*c*, 1).

(IIa, 17). As experiment "IIa, 14," but pyridine (1 ml) was added. The first crop (2·1 g) obtained after 1 day, had m.p. 168° with decomp., $[\alpha]_D^{20} = -165°$ (*c*, 1). Standing for several days gave an additional 0·31 g of less pure product, m.p. 162° (decomp.). Yield of crude product 80%.

(IIa, 18). As experiment "IIa, 1," but with a double amount of mannose (4·4 g, 2 moles), in less ethanol (20 ml) and with ammonium chloride (0·2 g) instead of hydrogen chloride catalyst. The crude product (2·3 g, 76·6%, m.p. 174° with decomp.) gave on washing with aqueous methanol pure *p*-tolyl-D-mannosyl-amine, with a loss of 16·3%; m.p. 184°, $[\alpha]_D^{21} = -178°$ (*c*, 1).

(IIa, 19). As experiment "IIa, 18," but less mannose (1·1 g, 0·5 mole) was employed. The crude product (1·2 g, 80%, based on mannose) had m.p. 160° (decomp.), $[\alpha]_D^{22} = -180°$ (*c*, 1). (Found: N, 5·22%). Yield of pure product was 73·6%.

N-p-Tolyl-D-mannosylamine by trans*-glycosylation from* N-p*-tolyl-*D*-galactosylamine and* D*-mannose*

(IIa, 20). N-*p*-Tolyl-D-galactosylamine (4·0 g, 1 mole) (m.p. 161–162°, $[\alpha]_D = -101°$) and anhydrous mannose (2·8 g, 1 mole) were refluxed in dry ethanol (120 ml) containing hydrogen chloride (0·028 g). Dissolution of the reagents occurred in 30 min. The crude product obtained on cooling was 1·1 g (27·5%), m.p. 180–181° (decomp.), $[\alpha]_D^{22} = -170°$ (*c*, 1). (Found: N, 5·25%).

(IIa, 21). As experiment "IIa, 20," but pyridine (4·0 ml) was added. After boiling for 5 min, crystallization set in on cooling (2·8 g, 70%); m.p. 180–181° (decomp.), $[\alpha]_D^{20} = -172°$ (*c*, 1) (c.f. 6). Yield of purified product was 66·2%. (Found: C, 57·4; H, 7·0; N, 5·1%).

N-p-*Tolyl*-D-*galactosylamine by* trans-*glycosylation from* N-p-*tolyl*-D-*glucosylamine and* D-*galactose*

(IIa, 22). The reaction mixture consisted of D-galactose (2·8 g, 1 mole), water (1 ml), methanol (40 ml) containing conc. hydrochloric acid [0·1 ml, and N-*p*-tolyl-D-glucosylamine (m.p. 112–113°, $[\alpha]_D^{20} = -96°$ (*c*, 1)]. The mixture was boiled for 10 min. When chilled in an ice-bath, the solution gave a crystalline precipitate (2·6 g, 65%), of m.p. 160–162°, $[\alpha]_D = -99·5°$ (*c*, 1·2). (Found: N, 5·05%). (Literature records:[6] m.p. 161–162°; $[\alpha]_D^{19} = -80°$ (in methanol). $[\alpha]_D^{20} = -101°$ (*c*, 1, in pryidine, own measurement). Mixed melting point determination gave no depression.

(IIa, 23). The experiment was the same as "IIa, 22," but pyridine (3 ml) was added and with 5 min reflux. The crystalline product (2·9 g, 72·5%) was very pure, m.p. 161°, $[\alpha]_D^{21} = -100°$ (*c*, 1). (Found: C, 57·1; H, 6·95; N, 5·11%).

The product gave homogenous galactosazone.

(IIa, 24). As experiment "IIa, 22," but without the addition of water, in the presence of dry hydrogen chloride catalyst (0·028 g). Dissolution required 40 min at the boiling point. The product (yields 25% and 28%, resp.) had m.p. 162°, $[\alpha]_D^{22} = -100°$ (*c*, 1·2).

N-p-*Bromophenyl*-D-*galactosylamine by* trans-*glycosylation from* N-p-*bromophenyl*-D-*glucosylamine and* D-*galactose*

(IIa, 25). The reaction mixture consisted of D-galactose (2·14 g, 1 mole), water (2 ml), pyridine (1 ml), methanol (20 ml), 3% hydrochloric acid (0·5 ml) and N-*p*-bromophenyl-D-glucosylamine (4·0 g, 1 mole) (m.p. 153°, $[\alpha]_D = -111°$ (*c*, 0·5, in pyridine); own measurements (see below). The mixture was refluxed for 5 min. The crystalline product (2·5 g), separated after 1 day, had m.p. 175° (decomp.); standing for several days gave but little additional precipitate (0·2 g) of m.p. 181° (decomp.). Yield 67·5%. $[\alpha]_D^{21} = -115°$ (*c*, 1). (Found: N, 4·07. $C_{12}H_{16}O_5NBr$ (334·1) requires N,4·2 0%). The glycoside gave a pure galactosazone.

Data of pure N-*p*-bromophenyl-D-galactosylamine are: m.p. 183–184°, $[\alpha]_D^{22} = -116·5°$ (*c*, 1). Own measurements (see below).

(IIa, 26). As experiment "IIa, 25," but with double amount of galactose (4·28 g, 2 moles). The yield of the crude product (3·1 g) was 77·5%, m.p. 173°, $[\alpha]_D^{20} = -114°$ (*c*, 1). (Found: N, 4·1%).

The product gave a pure galactosazone.

(IIa, 27). As experiment "IIa, 25," but without pyridine and with ammonium chloride (0·4 g) instead of hydrogen chloride catalyst. The mixture was refluxed for 15 min. Yield of the crude product (0·50 g, m.p. 177–178° and 0·36 g, m.p. 162–173°; $[\alpha]_D = -112°$ (*c*, 1), was 21·5%. (Found: N, 4·14; Br, 24·0, requires: N, 4·20; Br, 24·2%).

The product gave a pure galactosazone.

(IIa, 28). As experiment "IIa, 27," but pyridine (0·8 ml) was added. First crop (1·04 g) had m.p. 179° (decomp.), second crop (0·14 g), m.p. 168–172° (decomp.). $[\alpha]_D^{22} = -116°$ (*c*,1). Yield of crude product was 29·5%.

The product gave a pure galactosazone.

N-p-*Bromophenyl*-D-*glucosylamine*

p-Bromoaniline (6·0 g), and D-glucose (4·0 g) were refluxed for 30 min in methanol (50 ml), in the presence of concentrated hydrochloric acid catalyst (0·1 ml). On cooling, the crude product (5·2 g, 70%, m.p. 150°) separated, which was recrystallized from methanol (20 ml/5 g of product). The pure substance (3·3 g) had m.p. 153°, $[\alpha]_D = -111°$ (*c*, 0·5).

N-p-*Bromophenyl*-D-*galactosylamine*

p-Bromoaniline (2·0 g) and D-galactose (2·0 g) in 10% aqueous methanol (22 ml) was refluxed for 30 min in the presence of concentrated hydrochloric acid (1 drop). The crude product (2·85 g, 74%), separated on cooling, had m.p. 183–184°. It was recrystallized from 95% methanol; m.p. 184°, $[\alpha]_D^{22} = -116·5°$ (*c*, 1).

N-p-*Nitrophenyl*-D-*galactosylamine by* trans-*glycosylation from* N-p-*nitrophenyl*-D-*glucosylamine and* D-*galactose*

(IIa, 29). The reaction mixture consisted of N-*p*-nitrophenyl-D-glucosylamine (4·5 g, 1 mole)

[m.p. 184° $[\alpha]_D^{22} = -193°$ (*c*, 1·4)],[7] D-galactose (3·0 g, 1 mole), 96% ethanol (200 ml), and concentrated hydrochloric acid (0·2 ml). The mixture was refluxed for 15 min, complete dissolution occurred in the first 3 min. The solution was cooled, and the crude product (1·6 g, 35·5%) recrystallized from 75% aqueous methanol (30 ml) (0·67 g, 15%); m.p. 215° (decomp.), $[\alpha]_D = -185° \rightarrow 232°$ (*c*, 1·2) (Found: N, 9·51. Calc.: N, 9·34%). The product gave galactosazone. Literature[8] records for N-*p*-nitrophenyl-galactosylamine: m.p. 219°, $[\alpha]_D^{21} = -187 \rightarrow 248°$ (in anhydrous pyridine).

(IIa, 30). As experiment "IIa, 29," but pyridine (5 ml) was added. The time of refluxing was 5 min. The crude product [2·35 g, 50%, m.p. 170° (decomp.)] was recrystallized from 75% methanol to give a product of m.p. 210°, $[\alpha]_D^{20} = -183 \rightarrow 235°$ (*c*, 1). Yield of the purified substance was 34%. (Found, C, 47·92; H, 5·41; N, 9·39. Calc. for $C_{12}H_{16}O_7N_2$ (300·3): C, 48·07; H, 5·37; N, 9·34%).

Trans-*glycosylation Reactions belonging to Type* IIb

Trans-glycosylation of N-aryl-acetylglycosylamines and free aldoses.

N-p-*Tolyl*-D-*mannosylamine*

(IIb, 1). N-*p*-Tolyl-D-mannosylamine tetraacetate (4·5 g, 1 mole) and D-mannose (2·0 g, 1 mole) were refluxed in a mixture of 96% ethanol (20 ml), pyridine (1 ml), and concentrated hydrochloric acid (0·1 ml). Dissolution of the reagents took place in 10 min, and the mixture was boiled for an additional 5 min. After cooling and seeding, the solution solidified. On washing with aqueous methanol, pure N-*p*-tolyl-D-mannosylamine (78%) was obtained, m.p. 184°, $[\alpha]_D^{22} = -170°$ (*c*, 1). (Found: N, 5·28. Calc. 5·2%).

(IIb, 2). As experiment "IIb, 1," but without pyridine and with ammonium chloride (0·3 g, 0·5 mole) instead of hydrochloric acid catalyst. The time of refluxing was 30 min. On standing in a refrigerator, the crude product separated. It was washed with 75% aqueous methanol to give a product (64·5%), m.p. 184°, $[\alpha]_D = -171°$ (*c*, 1). (Found: N, 5·12%).

N-p-*Tolyl*-D-*mannosylamine and* 2:3:4:6-*Tetra-acetyl*-D-*glucose*

(IIb, 3). The experiment was carried out in the same way as "IIb, 1," except that a double amount of pyridine and four times as much hydrochloric acid were used. Yield of separated and purified *p*-tolyl-mannosylamine was 75% and 76%, respectively, as a result of two parallel experiments.

The mother liquor of this experiment was worked up for isolating the tetraacetyl glucose by evaporation under reduced pressure, and the residue was extracted with acetone; the acetone was distilled, the remaining material dissolved with water, and the aqueous solution extracted with chloroform. The solid residue from the chloroform solution was recrystallized from a small amount of a mixture of acetone and ethyl acetate: 61% and 42%, resp., yields of β-tetraacetyl glucose were obtained in two experiments; m.p. 118–120°, $[\alpha]_D^{22} = +29·2° \rightarrow +78·4°$ (*c*, 1, in alcohol). Literature[9] records, m.p. 118–120°, $[\alpha]_D^{22} = +2·19° \rightarrow +82·7°$ (in ethanol). The product contained no nitrogen. (Found: acetyl, 47·8%. Calc. 49·4%).

(IIb, 4). When experiment "IIb, 1," was repeated in the absence of pyridine, no *trans*-glycosylation reaction occurred.

(IIb, 5). When experiments "IIb, 1" or "IIb, 3" were tried without employing pyridine and hydrochloric acid catalyst, 89% of unreacted *p*-tolyl-D-glucosylamine tetraacetate was recovered after 20 min boiling, i.e. no *trans*-glycosylation reaction took place.

N^1-p-*Sulphamylphenyl*-D-*glucosylamine*

(IIb, 6). N^1-*p*-Sulphamylphenyl-D-glucosylamine tetraacetate (5·0 g, 1 mole) and D-glucose (3·0 g, 1 mole) were boiled for 15 min in ethanol (80 ml) containing water (2 ml) and hydrogen chloride (0·06 g). On standing in a refrigerator, the solution gave N^1-*p*-sulphamylphenyl-D-glucosylamine, in a small amount (0·5 g, 15%), but in high purity; m.p. 204°, $[\alpha]_D^{22} = -116°$ (*c*, 1). (Found: N, 8·27; S, 9·4. Calc. N, 8·4; S, 9·6%) (cf.[10]).

[7] R. Bognár and P. Nánási, *J. Chem. Soc.* 191 (1955); *Magyar Kémiai Folyóirat* **62**, 90 (1956).
[8] F. Weygand, W. Perkow and P. Kuhner, *Ber. Dtsch. Chem. Ges.* **84**, 194 (1951).
[9] E. Fischer and K. Delbrück, *Ber. Dtsch. Chem. Ges.* **42**, 2776 (1909)
[10] R. Bognár and P. Nánási, *J. Chem. Soc.* 1703 (1953); *Magyar Kémiai Folyóirat* **59**, 178 (1955).

N-p-*Tolyl*-D-*mannosylamine and tetraacetyl*-D-*mannose*

(IIb, 7). N-*p*-Tolyl-mannosyl tetraacetate (4·5 g, 1 mole), and D-mannose (2·0 g, 1 mole) were refluxed in 96% alcohol (20 ml), in the presence of pyridine (1 ml) and concentrated hydrochloric acid (0·1 ml). Complete dissolution occured in 5 min, and after an additional 5 min of boiling the mixture was allowed to stand at room temperature, then in a refrigerator for 2 hr, when N-*p*-tolyl-mannosylamine crystallized. (Experiment I: 1·26 g, 45·5%, m.p. 184°, $[\alpha]_D^{21} = -178°$ (*c*, 1·2); Found: N, 5·32. Calc.: N, 5·2. Experiment II: 63·5%, m.p. 183°, $[\alpha]_D = -175°$ (*c*, 1). Found: N, 5·16%).

The reddish-brown mother liquor was evaporated under reduced pressure until almost dry. The residue was extracted four times with 12 ml portions of ether, the ether solution was filtered, and mixed with light gasoline until the mixture became turbid. Inoculation at room temperature started crystallization.

Experiment I gave 36·6% tetraacetyl mannose of m.p. 95–96°, experiment II resulted in a yield of 54·5%, m.p. 96°, $[\alpha]_D^{21} = +27·5°$ (*c*, 1), $[\alpha]_D^{21} = +28·8$ (*c*, 1, in $CHCl_3$). The products contained no nitrogen. (Found: acetyl, 48·8%. Calc.: 49·4%). Literature[11] records m.p. 94° and 93°, $[\alpha]_D = +25·5$ and $+26·3°$ (both in chloroform).

N-p-*Tolyl*-D-*mannosylamine and tetraacetyl*-D-*galactose*

(IIb, 8). N-*p*-Tolyl-D-galactosylamine tetraacetate (2·25 g, 1 mole) and D-mannose (1·0 g, 1 mole) were boiled for 10 min in ethanol (8 ml), in the presence of pyridine (0·2 ml) and concentrated hydrochloric acid (0·1 ml). Crystallization of N-*p*-tolyl-mannosylamine started on cooling. The product (0·9 g, 65%) was filtered off, m.p. 182° (decomp.), $[\alpha]_D^{21} = -173°$ (*c*, 1). (Found: N, 5·12%).

The mother liquor was concentrated and the residue extracted with chloroform (20 ml). The chloroform solution, after treatment with activated carbon, was again concentrated under reduced pressure, and the remaining solid extracted with cold water. This water solution was shaken again with chloroform, the extract dried on Na_2SO_4, evaporated, and the residue recrystallized from a mixture of ether and light gasoline, to give a product (0·69 g, 38·5%) of m.p. 114°.

A repetition of the above purification and crystallization process gave tetraacetyl galactose (26%) of m.p. 118·5°, $[\alpha]_D = +52·1° \rightarrow 71°$ (in 4 hr; *c*, 1·2 in water). (Found: acetyl, 48·5%. Calc. for $C_{12}O_{20}O_{10}$ (348·3): 49·4%).

A second experiment gave the following results: Yield of N-*p*-tolyl-mannosylamine 64·5%; m.p. 182°. Yield of tetraacetyl-D-galactose 46·8%; m.p. 114°.

Literature[12] records for β-tetraacetyl galactose, m.p. 112–128°, $[\alpha]_D^{24} = +25° \rightarrow +76°$ (in H_2O).

Trans-*glycosylation Reactions belonging to Type* IIIa

Trans-glycosylation of two N-arylglycosylamines containing different arylamine and glycosyl parts.

N-p-*Nitrophenyl*-D-*galactosylamine by* trans-*glycosylation from* N-p-*nitrophenyl*-D-*glucosylamine and* N-p-*tolyl*-D-*galactosylamine*

(IIIa, 1). Dry N-*p*-tolyl-D-galactosylamine (2·7 g, 1 mole) (m.p. 154–155°; 161–162°; $[\alpha]_D = -101°$) and dry N-*p*-nitrophenyl-D-glucosylamine (3·0 g, 1 mole) (m.p. 183–184°, $[\alpha]_D = -202°$) were boiled in absolute ethanol (28 ml) containing dry hydrogen chloride (0·025 g). Complete dissolution was obtained in about 2 min, and a further 3 min of refluxing resulted in the beginning of crystallization. On cooling, 1·8 g crystalline material (60%) was obtained, m.p. 185–195°.

Recrystallization from 75% methanol and repeated washing gave a final yield of 42%, m.p. 217° (decomp.), $[\alpha]_D^{22} = -186°$ (*c*, 1·1, immediately after dissolution). (Found: C, 47·7; H, 5·42; N, 9·26. Calc. for $C_{12}H_{16}O_7N_2$ (300·3): C, 48·04; H, 5·37; N, 9·3%).

Pure galactosazone was obtained from the product.

(IIIa, 2). The experiment was carried out in the same way as "IIa, 1," but in the presence of pyridine.

[11] A. M. Gachokidze, *Z. Org. Chem.* **22**, 139 (1952); P. A. Levene and R. S. Tipson, *J. Biol. Chem.* **90**, 89 (1931).

[12] J. Compton and M. L. Wolfrom, *J. Amer. Chem. Soc.* **56**, 1157 (1934).

The reaction mixture consisted of N-*p*-tolyl-D-galactosylamine (4·0 g, 1 mole), N-*p*-nitrophenyl-D-glucosylamine (4·4 g, 1 mole), pyridine (1 ml) and anhydrous ethanol (50 ml) containing hydrogen chloride (0·05 g). The mixture was refluxed for 5 min. The separated crude product was recrystallized from 75% methanol to give a yield of 2·97 g (67·5%), m.p. 213° (decomp.), $[\alpha]_D^{21} = -189°$ (*c*, 1 immediately after dissolution). (Found: N, 9·2. Calc.: N, 9·3%).

The product gave a pure galactosazone.

(IIIa, 3). As experiment "IIIa, 1," but 2 moles of *p*-nitrophenyl-D-glucosylamine and a more dilute solution were employed.

The reaction mixture consisted of N-*p*-tolyl-D-galactosylamine (2·0 g, 1 mole) and N-*p*-nitrophenyl-D-glucosylamine (4·4 g, 2 moles) in anhydrous ethanol (60 ml) containing dry hydrogen chloride (0·03 g). The mixture was refluxed 3 min. The crude precipitates were recrystallized from 30 volumes of 75% methanol. Yield 55%, m.p. 210–213°, $[\alpha]_D^{24} = -188° \rightarrow -225°$ (*c*, 0·8 in 48 hr). (cf.[8]).

The product gave a pure galactosazone.

(IIIa, 4). As experiment "IIIa, 1," but without employing hydrogen chloride catalyst. In this case no *trans*-glycosylation could be detected, and the original glycosides were recovered by fractionated crystallization.

N⁴-p-*Sulphamylphenyl*-D-*glucosylamine*

(a) *By* trans-*glycosylation from* N⁴-p-*sulphamylphenyl*-D-*galactosylamine and* N-p-*tolyl*-D-*glucosylamine*. (IIIa, 5). The reaction mixture consisted of N⁴-*p*-sulphamylphenyl-D-galactosylamine (3·4 g, 1 mole) (m.p. 171–175°, $[\alpha]_D = -110°$)[9] and N-*p*-tolyl-D-glucosylamine (2·6 g, 1 mole) in anhydrous methanol (60 ml) containing dry hydrogen chloride (0·038 g). The mixture was boiled for 5 min. After separating a small amount (0·1 g, m.p. 201°) direct precipitation, the mother liquor gave a second crop (0·43 g) on the addition of ether. The combined crude products were recrystallized from dry methanol. Total yield of pure product was 15·5%, m.p. 198°, $[\alpha]_D^{22} = -112°$ (*c*, 0·8). (Found: N, 8·3; S, 9·7. Calc. for $C_{12}H_{18}O_7N_2S$ (334·34): N, 8·4; S, 9·6%). (cf.[10]).

The osazone test gave pure glucosazone.

Literature[7] records, for N⁴-*p*-sulphamylphenyl-D-glucosylamine, m.p. 202–204°, $[\alpha]_D^{22} = -115°$.

(IIIa, 6). As experiment "IIIa, 5," but in the presence of pyridine (0·7 ml). Yield 24%; m.p. 196° (decomp.), $[\alpha]_D = -113°$ (*c*, 1).

The product gave a pure glucosazone.

(IIIa, 7). As experiment "IIIa, 6," but 2 moles, of N-*p*-tolyl-D-glucosylamine were employed. Yield 27·5%; m.p. 198° (decomp,), $[\alpha]_D^{20} = -112°$ (*c*, 1).

The product gave pure glucosazone.

(IIIa, 8). As experiment "IIIa, 6," but 2 moles of N⁴-*p*-sulphamylphenyl-D-galactosylamine were employed. Excess N⁴-*p*-sulphamylphenyl-D-galactosylamine crystallized from the reaction mixture.

(b) *By* trans-*glycosylation from* N⁴-p-*sulphamylphenyl*-D-*galactosylamine and* N-(4-*carboxy*-3-*hydroxyphenyl*-D-*glucosylamine*. (IIIa, 9). The reaction mixture consisted of dry N⁴-*p*-sulphamylphenyl-D-galactosylamine (5·0 g, 1 mole) (m.p. 171–174°) dry N-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine (5·0 g, 1·05 moles) (m.p. 142°, $[\alpha]_D = -134°$ [19]), ammonium chloride (0·2 g, 0·3 mole), and anhydrous methanol (50 ml). The reaction mixture was boiled for 30 min. Ether was admixed to the cooled solution until it became turbid, and the precipitated material was recrystallized from methanol to give 0·91 g product (18·2%); m.p. 201° (decomp.), $[\alpha]_D^{22} = -115°$ (*c*, 1). (Found: N, 8·27; S, 9·7. Calcd.: N, 8·4; S, 9·6%).

(IIIa, 10). As experiment "IIIa, 9," but in the presence of pyridine (1·5 ml), and with hydrogen chloride (0·05 g) instead of ammonium chloride catalyst. Cooling in an ice-bath gave a direct separated crop (20%); m.p. 190° (decomp.), $[\alpha]_D^{20} = -113°$ (*c*, 1).

The product gave a pure glucosazone.

Trans-*glycosylation belonging to Type* IIIb

Reaction of aryl-acetylglycosylamine with non-acetylated arylglycosylamine.

N⁴-p-*Sulphamylphenyl*-D-*glucosylamine*

Trans-*glycosylation of* N⁴-p-*sulphamylphenyl*-D-*glucosylamine tetraacetate and* N-p-*tolyl*-D-*glucosylamine*

(IIIb 1). N^4-*p*-sulphamylphenyl-D-glucosylamine tetraacetate (5·0 g, 1 mole) and N-*p*-tolyl-D-glucosylamine (5·4 g, 2 moles) were refluxed for 15 min in 96% ethanol (100 ml) in the presence of 3% hydrochloric acid (1 ml). Scratching started crystallization in about 2 hr. The mixture was then gently warmed (40°–50°) in order to prevent precipitation of N^4-*p*-sulphamylphenyl-D-glucosylamine tetraacetate. The product (3·0 g, 90%), separated at room temperature, consisted of pure N^4-*p*-sulphamylphenyl-D-glucosylamine; m.p. 202°, $[\alpha]_D^{22} = -121°$ (*c*, 1, in water). (Found: N, 8·32; S, 9·42. Calc. for $C_{12}H_{18}O_7N_2S$ (334·34): N, 8·4; S, 9·6%). (cf.[10]).

Acknowledgements—We are grateful to Mrs. É. Rákosi for the analyses, and to the Hungarian Academy of Sciences for support.

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ZUR DARSTELLUNG *o*-CHINOIDER KOHLENWASSERSTOFFE UND DEREN VERHALTEN GEGENÜBER PHILODIENEN

K. ALDER† und M. FREMERY[1]

(*Received* 14 *November* 1960)

Zusammenfassung—Es wird eine Methode beschrieben, die gestattet *o*-ständige Biradikaletts intermediär darzustellen.

Diese äusserst reaktionsfähigen Körper vermögen zahlreiche Additionsreaktionen mit anderen aktivierten Komponenten einzugehen; so wurde gefunden, dass sie auch dem Additionsprinzip der Dien-Synthese zugänglich sind, das dabei zu neuen Tetralin-Derivaten führt. Die Darstellung dieser intermediären Systeme erfolgt durch eine quantitativ verlaufende Brom-Abspaltung aus Dibromiden mit *o*-ständigen Methylen-bromid-Gruppen.

Abstract—A method for the formation of intermediary *o*-biradicaletts is described. These extreme instable hydrocarbons undergo readily addition reactions with other activated components; thus it was found that the addition principles of the Diels–Alder reaction can be applied, which leads to the formation of tetralin-derivatives.

The preparation of these intermediary systems is performed by a quantitative bromine-cleavage from *o*-methylene-bromides.

IM Jahre 1945 führten Namiot *et al.*[2] unter Anwendung des Heitler-London'schen Molecular Orbital-Näherungsverfahrens Berechnungen durch, die in quantitativer Hinsicht Einblick in die energetischen Zustände der *o*-, *m*- und *p*-Chino-dimethane ermöglichen. Der Vergleich der Energieinhalte dieser Körper ergab, dass im Falle des *o*- und *p*-Chino-dimethans aufgrund der Konjugation eine relativ hohe Resonanzenergie besteht, die fast an diejenige des aromatischen Systemes heranreicht. Die völlige Instabilität dieser chinoiden Kohlenwasserstoffe lässt sich auf die leichte Verschiebbarkeit der π-Elektronen über die Konjugation zurückführen, welche eine stabilisierende Umlagerung zum aromatischen System -unter Polymerisation-ermöglicht.

Diatkin und Syrkin[3] ermittelten auch die Erregungsenergien des Singulett und Triplett-Zustandes vom *o*-und *p*-Chino-dimethan und entnahmen aus den Ergebnissen, dass neben den chinoiden Doppelbindungssystemen mit antiparallelen Spinmomenten, auch biradikalische Systeme mit parallelen Spinmomenten möglich sind, da deren Energieinhalt in der gleichen Grössenanordnung liegt.

Experimentell lässt sich das *o*-Chino-dimethan in verschiedener Weise darstellen und durch sein Polymerisat charakterisieren.

So wurde die Abspaltung von Brom aus ω,ω'-Dibrom-*o*-xylylen mit Natrium[4] als auch Grignard-Reaktionen mit den entsprechenden Alkoxy-halogeniden[5] beschrieben sowie vor allem Pyrolysen entweder mit *o*-Xylol[6] oder mit ω,ω'-Dijod-*o*-xylylen[7] durchgeführt.

[1] Dissertation 1958, ausgeführt im Chemischen Institut der Universität Köln. (Jetzige Anschr.: Research Dept., American Oil Co., Whiting, Indiana, U.S.A.)
[2] A. J. Namiot, M. E. Diatkin u. I. K. Syvkin, *C. R. Acad. Sci. URSS* **48**, 267 (1945).
[3] M. E. Diatkin u. I. K. Syrkin, *Acta Physiocochim. URSS* **21**, 421 (1946).
[4] W. Baker, *J. Chem. Soc.* 27 (1945).
[5] F. G. Mann, *J. Chem. Soc.* 2826 (1954).
[6] A. Szwarc, *J. Chem. Phys.* **16**, 128 (1948).
[7] G. Farmer, *J. Chem. Phys.* **23**, 403 (1955).

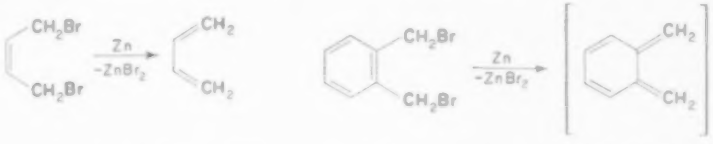
In diesen Untersuchungen trat die Reaktionsfreudigkeit des instabilen Kohlenwasserstoffes lediglich in Form von Polymerisationsvorgängen in Erscheinung. Deshalb erschien es im besonderen Masse interessant, Additionsreaktionen mit anderen Komponenten unter Bildung wohldefinierter Addukte, zu untersuchen.

Die günstigste Annäherung hierzu erschien in der Darstellung des chinoiden Körpers gleich in der Gegenwart der zweiten Additionskomponente, so dass er im intermediären Zustand an die andere Komponente addiert. Dies kann aber nur dann zu Ergebnissen führen, wenn die Additionsgeschwindigkeit mindestens in der Grössenanordnung der Polymerisationsgeschwindigkeit des *o*-Chino-dimethans liegt, eine Bedingung, die durch geeignete Konzentrationswahl der Komponenten sowie durch genügend aktivierte Doppelbindungen der Addenden leicht erfüllbar ist.

In der vorliegenden Untersuchung wurde hauptsächlich das Prinzip der Dien-Synthese als Additionsreaktion angewendet, indem Philodiene als zweite Additionskomponente mit den intermediären *o*-chinoiden Systemen-resp. Biradikalen umgesetzt werden.

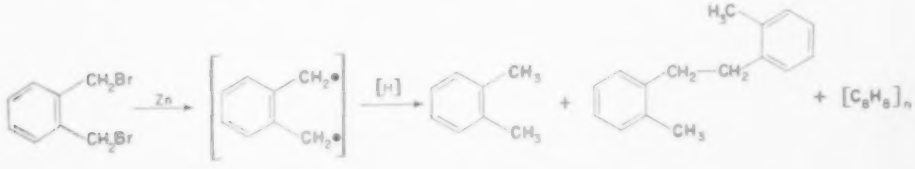
Da die bekannten Methoden zur Darstellung des *o*-Chino-dimethans den Voraussetzungen für die Additionsreaktion nicht genügen, wurde eine Methode entwickelt, die einerseits eine intermediäre Bildung des Kohlenwasserstoffes gestattet, andererseits die beigefügte zweite Additionskomponente chemisch unverändert lässt.

Die Reaktion beruht auf ein Darstellungsprinzip für Butadien aus 1,4-Dibrombuten-2, bei dem das Dibromid in Äthanol mit Zink umgesetzt wird.[8] Die gleichen



Bedingungen wurden auf ω,ω'-Dibrom-*o*-xylylen angewendet, wobei sich jedoch ergab, dass bei schwach polaren Lösungsmitteln und niedriger Temperatur die Bromabspaltung mit Zinkstaub in unbefriedigender Ausbeute verlief. Hingegen konnte eine totale Entbromierung in Gegenwart stark polarer Lösungsmittel wie Essigsäure oder Dimethyl-formamid erzielt werden.

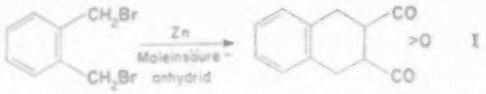
Zunächst wurde das *o*-Chino-dimethan ohne Gegenwart eines Philodienes dargestellt. Die Bromabspaltung aus dem entsprechenden Dibromid erfolgte in hoher Verdünnung in Essigsäure als Lösungsmittel mit Zinkstaub bei 20°. Aus dem Reaktionsgemisch konnte *o*-Xylol, α,β-Di-*o*-tolu-äthan sowie ein höheres Polymerisat isoliert werden. Die Bildung der beiden erstgenannten Reaktionsprodukte erfolgte durch die reduzierende Wirkung des Zink-Essigsäure-systemes auf den—durch die Entbromierung gebildeten—aktiven Kohlenwasserstoff, was auf einen radikalischen Reaktionsmechanismus hinweist.



[8] J. Thiele, *Liebigs Ann.* **308**, 339 (1899).

Bei Anwendung des radikalisch indifferenten Dimethyl-formamids als Lösungsmittel wurde unter den gleichen Bedingungen in theoretischer Ausbeute reines höheres Polymerisat gebildet. Dieses Lösungsmittel geht bei Temperaturen unter 60° keine Nebenreaktionen ein und erweist sich für die Reaktionen als besonders gut geeignet.

Bei Anwesenheit von Maleinsäure-anhydrid als zweite Additionskomponente verläuft die Bromabspaltung in Dimethyl-formamid durch Zink exotherm unter Bildung des Adduktes I in 93% Ausbeute.



I

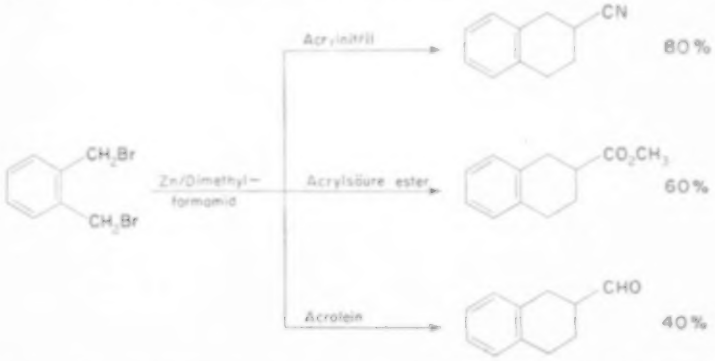
Das Ergebnis dieser Addition wurde durch einen Parallelversuch mit einem anderen Ausgangsmaterial für die Darstellung des intermediären *o*-Chino-dimethans geprüft:

Die Beobachtung einer totalen Polymerisation des Benzo-cyclobutens bei Temperaturen über 150° gab einen Hinweis dafür, dass mit grosser Wahrscheinlichkeit der Vierring zwischen C–1 und C–2 unter Isomerisierung zum *o*-Chino-dimethan aufspaltet.

So wurde das Benzo-cyclobuten in Gegenwart von Maleinsäure-anhydrid auf 150° erhitzt, wobei tatsächlich eine Addition unter Bildung desselben Adduktes wie vom ω,ω'-Dibrom-*o*-xylylen eintritt.

In beiden Fällen entspricht der Schmelzpunkt des gewonnenen Tetralindicarbonsäure-anhydrids seiner reinen *cis*-Form.[9]

Unter den gleichen Bedingungen der Bromabspaltung in Gegenwart von Maleinsäure-anhydrid wurde Acryl-nitril, Acrylsäure-methylester sowie Acrolein als Philodien

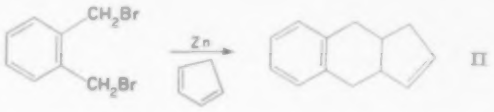


angewendet. Die Reaktionen ergaben Tetralin-2-nitril, Tetralin-2-carbonsäure-methylester und Tetralin-2-aldehyd als wohldefinierte Addukte in geringeren Ausbeuten.

Der Vergleich der Ausbeuten weist auf die schon angedeutete Notwendigkeit einer genügenden Aktivierung der C,C-Doppelbindung im Philodien hin. So aktiviert die Aldehyd-Gruppe das Additionszentrum im weitaus geringerem Masse wie z.B. die Anhydrid-Gruppe des Maleinsäure-anhydrids. Dadurch wird die Konkurrenzreaktion—die Polymerisation des *o*-Chino-dimethans—trotz Anwendung des Verdünnungsprinzips begünstigt. Unter diesem Gesichtspunkt der Aktivierung des

[9] R. D. Haworth, *J. Chem. Soc.* 1321 (1940).

C,C-Additionszentrums erschien es interessant, einen typischen Vertreter der Diene als Philodien anzuwenden. So ergab die Addition mit Cyclopentadien unter den beschriebenen Reaktionsbedingungen, dass trotz der Konjugation eine hinreichende Aktivierung der Doppelbindungen für philodiene Reaktionen vorliegt: Das Addukt II konnte in 40% Ausbeute als 5,6-Benzo-4,7-dihydroinden isoliert werden.



II

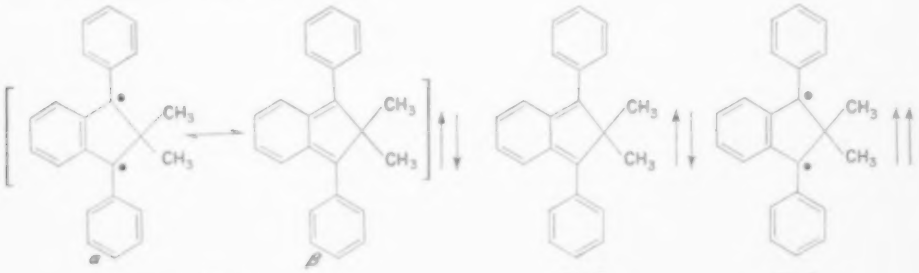
Bisher wurden nur diejenigen Philodiene beschrieben, deren addierende Zentren jeweils eine C,C-Doppelbindung besitzen. Eine Untersuchung des Verhaltens der Philodiene mit andersartigen aktiven Additionszentren, wie die der N,N-Doppelbindung des Azo-dicarbonsäure-dimethylesters oder die C,C-Dreifachbindung des Acetylen-dicarbonsäure-dimethylesters ergab unerwarteter Weise eindeutig negative Resultate: In beiden Fällen trat keine Addition ein, als Reaktions-endprodukt wurde lediglich das Polymerisat des *o*-Chino-dimethans isoliert.

Die beschriebene Untersuchung der Additionen des *o*-Chino-dimethans lässt die Existenz des intermediären Kohlenwasserstoffes als *o*-chinoides System, Biradikal oder Biradikalett unentschieden. So galt es, für das experimentelle Studium, einen Kohlenwasserstoff herzustellen, der dasselbe Strukturprinzip des *o*-Chino-dimethans, aufweist aber keine stabilisierende Polymerisation sowie intramolekulare Umlagerung einzugehen vermag.

Dazu erschien das 1,3-Diphenyl-2,2-dimethyl-iso-inden IV als besonders gut geeignet. Dieser Kohlenwasserstoff lässt sich—ausgehend vom 1,3-Diphenyl-1,3-dibrom-2,2-dimethyl-indan III unter denselben Reaktionsprinzip darstellen, wied as *o*-Chino-dimethan.

So wurde zunächst die Bromabspaltung in der beschriebenen Methode—ohne Gegenwart eines Philodiens—vorgenommen. Bei der Aufbereitung des aktiven Kohlenwasserstoffes konnte jedoch die Anwendung von Wasser nicht vermieden werden, es erfolgte dabei in momentaner radikalischer Reaktion eine Absättigung unter Bildung des Carbinols V als Addukt. Eine Umgehung dieser Nebenreaktion ist möglich durch die Anwendung von Zink-amalgan in Toluol bei 100°. So konnte das dabei resultierende, stark fluoreszierende Isoinden-Derivat IV als verhätnismässig stabiles, hochviskoses Öl durch Hochvakuum-Destillation isoliert werden.

Die Struktur des gewonnenen 1,3-Diphenyl-2,2-dimethyl-isoindens wäre unter den drei Möglichkeiten zu diskutieren:



IV A IV B IV C

Das Ultraviolett-Spektrum dieses Körpers weist weder auf ein konjugiertes System-gemäss IVB, noch auf isolierte Phenyl-Gruppen-gemäss IVC hin. Danach liegen die echten Systeme eines *o*-chinoiden Isoindens sowie eines Biradikals nicht vor.

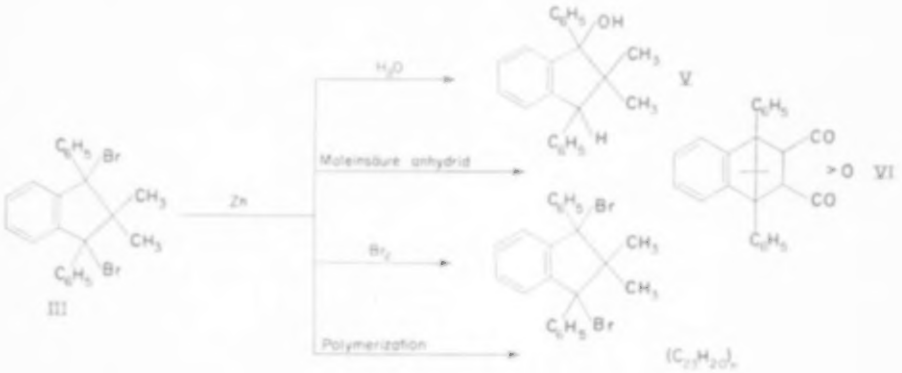
Das Ergebnis der magnetochemischen Untersuchung entspricht eindeutig einem diamagnetischen Verhalten, womit die Existenz eines echten Biradikals auszuschliessen ist.

Die chemische Untersuchung des aktiven Kohlenwasserstoffes ergab, dass bei seiner Bromierung momentan ein Moläquiv. Brom aufgenommen wird unter Bildung eines Dibromides, welches mit dem Ausgangsbromid III identisch ist. Dies weist darauf hin, dass keine Umlagerung in dem Kohlenwasserstoff stattgefunden hat.

In Gegenwart von Maleinsäure-anhydrid setzt bei 25° unter Entfärbung eine Addition ein, wobei das Addukt VI in guter Ausbeute gebildet wird.

Die Anwendung von Azo-dicarbonsäure-ester sowie Acetylen-dicarbonsäure-ester als Philodien verlief auch hier erfolglos.

Der Kohlenwasserstoff polymerisiert bei 25° erst nach längerer Aufbewahrung.



Bei der Zusammenfassung dieser chemischen und physikalischen Feststellungen ergibt sich unmittelbar, dass der Kohlenwasserstoff IV tatsächlich als mesomeriestabilisiertes Biradikalett IVA vorliegt. Dies steht in guter Übereinstimmung mit den von E. Müller[10] angestellten Überlegungen, da die Struktur des Kohlenwasserstoffes allen Voraussetzungen für eine Resonanzstabilisation entspricht. (So ist auch die Unbestimmbarkeit seines U.V.-Spektrums durch die Resonanz zwischen den Grenzstrukturen α und β unter Bildung des strukturell nicht "fixierbaren" Biradikaletts IVA verständlich.)

Die Identität des Strukturprinzipes zwischen dem Isoinden Derivat IVA und dem *o*-Chino-dimethan lässt die sichere Annahme zu, dass auch das Letztere als Biradikalett vorliegt; seine Kurzlebigkeit ist lediglich auf die Abwesenheit der resonanzstabilisierenden und relativ grossvolumigen Substituenten zurückzuführen.

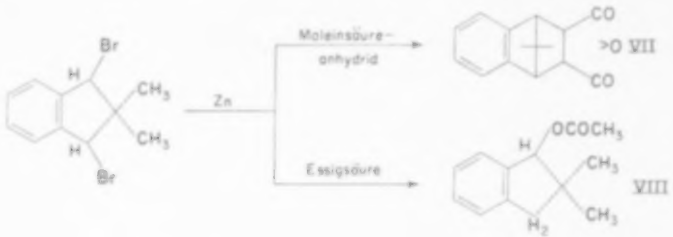
Unter Anwendung weiterer aktiver Kohlenwasserstoffe analoger Struktur wurde die Untersuchung des Verhaltens des Biradikalett-Systemes gegenüber Philodiene fortgesetzt, indem methyl-substituierte Isoindene und vor allem das Isoinden selbst angewendet wurden.

[10] E. Müller, *Fortschr. Chem. Forschg.* **1**, 375 (1949); *Angew. Chem.* **64**, 233 (1952).

Hierzu erschien zunächst die Brom-Abspaltung aus 1,2,2,3-Tetramethyl-1,3-dibrom-indan sowie aus 2,2-Dimethyl-1,3-dibrom-indan unter denselben Bedingungen wie bei dem ω,ω'-Dibrom-*o*-xylylen, naheliegend.

In beiden Fällen führten die Reaktionen zu einer momentanen 100 proz. Polymerisation der intermediär gebildeten Isoinden-Derivate. Hinsichtlich des 1,2,2,3-Tetramethyl-isoindens ist dies besonders bemerkenswert, wenn man seine geringe Stabilität mit der des weitgehend analogen 1,3-Diphenyl-2,2-dimethyl-isoindens vergleicht. Dies gibt wieder ein Hinweis dafür, dass die Phenyl-Gruppen in 1,3-Stellung nicht nur sterisch polymerisations-hindernd wirken, sondern auch auf-grund der aromatischen Struktur eine entscheidende Resonanzstabilisation verursachen.

Die Umsetzung des intermediär gebildeten 2,2-Dimethyl-isoindens mit Maleinsäure-anhydrid in Dimethyl-formamid führt in 75% Ausbeute zu dem Addukt VII sowie in Essigsäure zu dem 1-Acetoxy-2,2-dimethyl-indan VIII.



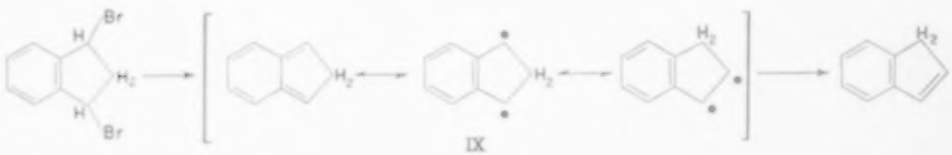
Die Bildung des Acetoxy-Derivates ist bemerkenswert, da sie vornehmlich auf einen ionischen Reaktionsmechanismus zurückzuführen ist. Dies schliesst jedoch die Existenz des intermediären 2,2-Dimethyl-isoindens als Biradikalett keineswegs aus.

Besonders interessant erschien nun die Untersuchung des Verhaltens des unsubstituierten Isoinden-Körpers, der in seiner 2-Stellung zwei Wasserstoffatome (die aufgrund ihrer leichten Verschiebbarkeit Ursache zahlreicher Umlagerungs-reaktionen sein können), enthält, da hierbei zumindest ein weiterer Hinweis für die—noch nicht eindeutig geklärte—Reaktionsweise des Indens gegenüber Philodienen zu erwarten war.

Die Brom-Abspaltung erfolgte wieder nach der beschriebenen Methode unter Anwendung von Dimethyl-formamid als Lösungsmittel.

Das resultierende Reaktionsprodukt enthielt neben 35% Polymerisat den Kohlenwasserstoff Inden.

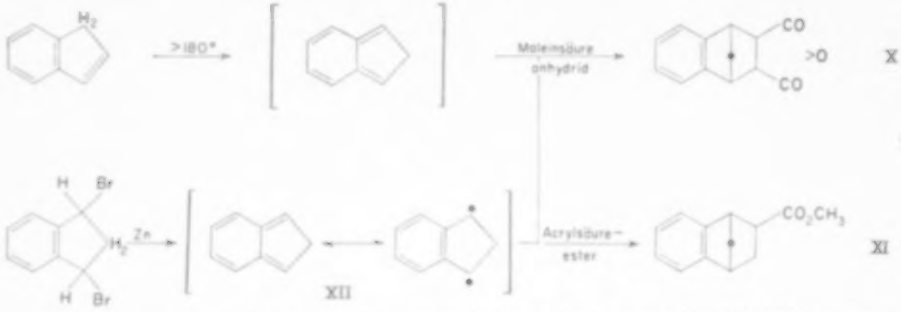
Seine Bildung kann durch eine Wasserstoff-Verschiebung in dem radikalischen Anteil des instabilen Biradikaletts IX erklärt werden:



IX

Die Durchführung der Brom-Abspaltung in Gegenwart von Maleinsäure-anhydrid ergab in 47% Ausbeute das bereits bekannte Addukt X. Seine früher beschriebene

Darstellung[11] verläuft aus der Addition von Inden mit Maleinsäure-anhydrid bei hoher Reaktionstemperatur, und der Additionsvorgang wurde über eine Isomerisierung des Indens bei hohen Temperaturen zum chinoiden Isoinden formuliert.



Zur weiteren Anwendung der—bisher nur beim Maleinsäure-anhydrid bekannten—1,3-Addition des Indens aus seiner Isoform, wurde die Brom-Abspaltung in Gegenwart von Acrylsäure-methylester durchgeführt. Dabei bildet sich in 20% Ausbeute tatsächlich der 1,4-Endomethylen-tetralin-2-carbonsäure-methylester XI.

Die Ausführung desselben Reaktionsprinzips mit Acetylen-dicarbonsäure-ester sowie Azo-dicarbonsäure-ester als Philodien führte wieder zu keiner Addition. Ähnlich verhält sich das Ergebnis beim Erhitzen von Inden mit Acetylen-dicarbonsäure-ester auf 180°, bei der die Isomerisierung zum chinoiden Isoinden einsetzen sollte.[12] Da hier nach allen bisherigen Erfahrungen eine Diels–Alder-Addition bei dem stark aktivierten *o*-chinoiden Tetraen-System unbedingt eintreten müsste, liegt es nahe anzunehmen, dass das Isoinden nicht als ein echtes chinoides System vorliegt, sondern auch bei Temperaturen über 150°—wie bei der Brom-Abspaltung bei 20°—als ein Biradikalett XII auftritt. Dieser mesomere Zustand scheint jedoch—wie beim *o*-Chino-dimethan sowie 1,3-Diphenyl-2,2-dimethyl-isoinden—einer Diels–Alder Addition mit den letztgenannten Philodienen einen erheblichen Widerstand zu leisten, sodass hier Konkurrenzreaktionen den Vorrang haben.

Das vielseitige Verhalten des Indens gegenüber den verschiedenen Philodienen ist somit nicht—wie öfters angenommen—auf den Kohlenwasserstoff selbst zurückzuführen, sondern eher auf die verschiedene Additionsweise der Philodiene.

EXPERIMENTELLER TEIL

(1) *Brom-Abspaltung in Essigsäure*

20 g ω,ω-Dibrom-*o*-xylylen[13] werden in 150 cm³ Eisessig (destilliert über $KMnO_4$) gelöst und die Lösung innerhalb 6 Stdn. zu 500 cm³ Eisessig und 3 g Zinstaub[14] bei 20° unter kräftigem Rühren eingetropft. Pro Stunde erfolgt eine weitere Zugabe von je 1 g Zinkstaub. Nach Ablauf der Reaktion wird vom überschüssigem Zink abfiltriert und das Filtrat mit 1,2 L Wasser verdünnt, wobei das Reaktionsprodukt als Öl ausfällt. Anschliessend wird ausgeäthert, die ätherische Lösung gereinigt, der Äther abdestilliert und der Rückstand i. Vak. destilliert.

Dabei erhält man zwei Fraktionen:

o-Xylol (Identifiziert durch Siedepunkt und Brechungsindex) Ausbeute 40%.

[11] K. Alder u. F. Pascher, *Ber. Dtsch. Chem. Ges.* **75**, 1501 (1942).
[12] Wohl verläuft hier -bei niedrigeren Temperaturen- eine Addition nach einem völlig verschiedenen Mechanismus. (M. Dollhausen, Dissertation 1958, Chem. Inst. d. Universität Köln.)
[13] Darstellung gemäss: E. F. Atkinson, *J. Chem. Soc.* **91**, 1696 (1907).
[14] Der Zinkstaub wird in allen Versuchen erst durch Aufschlämmen in einer gesättigten NH_4Cl—Lösung aktiviert.

Sowie α,β-Di-o-tolu-äthan. Schmp. 63° (aus Ligroin) Ausbeute 15%.
(Gef.: C, 91·4, 91·5; H, 8·8, 8·7. Ber. für $C_{16}H_{16}$: C, 91·4; H, 8·6).
Der Rückstand-etwa 40%-besteht aus bromfreiem Polymerisat.

(2) *Brom-Abspaltung in Dimethyl-formamid*

20 g Dibromid werden in 100 cm³ Dimethyl-formamid (wasserfrei!) gelöst und die Lösung innerhalb 6 Stdn. zu 500 cm³ Dimethyl-formamid und 3 g Zinkstaub bei 20° unter kräftigem Rühren eingetropft. Pro Stunde erfolgt eine weitere Zugabe von je 1 g Zinkstaub. Nach Ablauf der Reaktion wird vom überschüssigem Zink über Kieselgur abfiltriert, das Filtrat in 1,2 L Wasser, 10 cm konz. HCl sowie 100 cm³ Äther verdünnt und anschliessend mehrmals ausgeäthert. Das in üblicher Weise isolierte Reaktionsprodukt besteht aus bromfreiem Polymerisat (ohne destillierbare Bestandteile).

(3) *Addition mit Maleinsäure-anhydrid*

23 g reines Maleinsäure-anhydrid werden in 500 cm³ Dimethyl-formamid gelöst, die Lösung auf 0° gekühlt und unter Rühren 4 g Zinkstaub zugefügt. Dabei tritt unter Erwärmung eine Braunfärbung ein (wahrscheinlich eine Komplex-bildung). Anschliessend wird wieder bei 20° eine Lösung von 20 g Dibromid und 7 g Maleinsäure-anhydrid in 100 cm³ Dimethyl-formamid innerhalb 6 Stdn. zugetropft. Pro Stunde erfolgt eine weitere Zugabe von je 1 g Zinkstaub. Das Reaktionsgemisch wird schliesslich zur Abtrennung vom überschüssigem Zink durch Kieselgur filtriert, in 1,2 L Wasser, 10 cm³ HCl sowie 100 cm³ Äther verdünnt und darauf mehrmals ausgeäthert. Nach Neutralisation und Trocknung ($MgSO_4$) wird der Äther abdestilliert, wobei das Addukt I kristallin ausfällt.
(Gef.: C, 71·2, 71·1; H, 5·1, 5·1. Ber. für $C_{12}H_{10}O_3$ C, 71·3; H, 5·0).
Schmp. 189° (aus Essigester) Ausbeute 93%.

(4) *Benzo-cyclo-buten als Ausgangssubstanz für o-Chino-dimethan*

Ein Gemisch von 1,2-Dibrom-benzo-cyclobuten sowie 1,2-Dijod-benzo-cyclobuten wurde nach der Vorschrift von Cava[15] dargestellt.
Schmp. 48° (IX aus Eisessig, IX aus Ligroin).
Zur Darstellung des Kohlenwasserstoffes werden 50 g Di-halogenid in 500 cm³ wasserfreiem Tetra-hydro-furan gelöst und bei 60° zu 200 cm³ Tetra-hydro-furan und 20 g $LiAlH_4$ (grosser Überschuss erforderlich) innerhalb 5 Stdn. unter Rühren zugetropfr. Anschliessend erhitzt man zwei Stdn. unter Rückfluss und zersetzt danach den LiAl-Komplex durch Zugabe der äquivalenten Menge Wasser bei 10°. Der anorganische Niederschlag lässt sich leicht abfiltrieren, sodass das Filtrat direkt im Halbvakuum eingeengt werden kann. Der Rückstand enthält neben dem Kohlenwasserstoff noch Wasser und Tetra-hydro-furan. Deshalb wird wenig Wasser zugegeben, viermal ausgeäthert und der Extrakt in üblicher Weise aufgearbeitet; die erste Destillation des gewonnenen Benzo-cyclobutens erfolgt über Natrium.
$Sdp._{150}$: 97° (Drehband), Identifizierung durch Vergleich der charakteristischen I.R.-Bande mit authentischem Produkt.
(Gef.: C, 92·2, 92·0; H, 7·8, 7·9. Ber. für C_8H_8: C, 92·3; H, 7·7).
Addition mit Maleinsäure-anhydrid. 5 g Benzo-cyclobuten werden zusammen mit 6 g Maleinsäure-anhydrid in 10 cm³ Benzol ca. 24 Stdn. in einem Bombenrohr auf 150° erhitzt. Nach Abkühlung kristallisiert das Addukt I in groben Nadeln aus.
Schmp. 189° (aus Essigester) Ausbeute 80%.
(Gef.: C, 71·2, 71·3; H, 5·2, 5·1. Ber. für $C_{12}H_{10}O_3$: C, 71·3; H, 5·0).
Der Mischschmelzpunkt mit dem *o*-Chino-dimethan-Addukt sowie mit einem authentischen Produkt[9] ergibt keine Depression.
Eine Addition des Benzo-cyclobutens mit Azo-dicarbonsäure-dimethylester findet bei 150–180° nicht statt.[16]

(5) *Addition mit Acrolein. Bildung von Tetralin-2-aldehyd*

20 g frisch destilliertes Acrolein werden in 500 cm³ Dimethyl-formamid gelöst und 3 g Zinkstaub zugefügt. Zu diesem Gemisch wird bei 20° unter Rühren eine Lösung von 20 g *o*-Dibrom-xylylen in

[15] M. P. Cava, *J. Amer. Chem. Soc.* **79**, 1701 (1957).
[16] Bei der Abspaltung des Halogens aus dem 1,2-Dihalogen-benzo-cyclobutens durch Zink in Gegenwart von Maleinsäure-anhydrid—wie unter (3) beschrieben—tritt lediglich eine Dimerisierung des intermediär gebildeten Benzo-cyclobutadiens[15] ein.

100 cm³ Dimethyl-formamid innerhalb 6 Stdn. eingetropft und weiter verfahren, wie unter (3) beschrieben. Der unter Stickstoff destillierte Aldehyd ist oxydabel und wird in Form stabiler Derivate charakterisiert.

Ausbeute des Tetralin-2-aldehyd: 40% (gelbes Öl).

Semicarbazon. Schmp. 194° (aus Methanol).

(Gef.: C, 67·0, 66·9; H, 7·2, 7·2. $C_{12}H_{15}N_3O$ entspr.: C, 66·3; H, 7·0).

Phenylhydrazon. Schmp. 174° (aus Essigester).

(Gef.: C, 82·5, 82·2; H, 7·6, 7·7. $C_{17}H_{18}N_2$ entspr.: C, 81·6; H, 7·3).

Der Destillationsrückstand bestehz aus Polymerisat.

(6) *Addition mit Acrylsäure-methylester. Bildung von Tetralin-2-carbonsäure-methylester*

Arbeitsweise wie unter (5) beschrieben. Das isolierte Addukt ist ein farbloses, stark nach Eukalyptus riechendes Öl. $Sdp._{0,02}$: 70°. Ausbeute: 60%.

(Gef.: C, 75·8; H, 7·4. $C_{12}H_{14}O_2$ entspr.: C, 75·8; H, 7·4).

Die Dehydrierung des Adduktes zum Naphthalin-β-carbonsäure-methylester erfolgt mit der für 4 H äquivalenten Menge Schwefel bei 190°. Nach Beendigung der Schwefelwasserstoff-Entwicklung wird das kristalline Produkt i. Vak. destilliert und aus Methanol umkristallisiert. Schmp. 75°. Im Gemisch mit einem authentischen Produkt erfolgt keine Schmelzpunkterniedrigung.

(7) *Addition mit Acryl-nitril. Bildung von Tetralin-2-nitril*

Arbeitsweise wie unter (5) beschrieben. $Sdp._{0,15}$: 92°. Das Destillat kristallisiert spontan. Schmp. 55° (aus Ligroin u. Essigester). Ausbeute: 80%.

(Gef.: C, 84·2, 84·4; H, 7·2, 7·3. $C_{11}H_{11}N$ entspr.: C, 84·0; H, 7·1).

Weitere Belegung durch U.V.-sowie I.R.-Spektrum.

(8) *Addition mit Cyclopentadien. Bildung von 5,6-Benzo-4,7-dihydro-inden* (II)

Arbeitsweise wie unter (5) beschrieben. $Sdp._3$: 98°. Ausbeute 40%.

(Gef.: C, 92·0, 92·1; H, 8·4, 8·3. $C_{13}H_{14}$ entspr. C, 91·7; H, 8·3).

Weitere Belegung durch U.V. -und I.R.-Spektrum sowie partielle Hydrierung.

(9) *Darstellung des 1,3-Diphenyl-2,2-dimethyl-1,3-dibrom-indan* (III)

20 g 2,2-Dimethyl-indandion-1,3 (hergestellt nach der Vorschrift von Wislicenus[17]) werden in 100 cm³ Äther gelöst und bei 0° zu einem 4-mol-äquivalenten (zweifacher Überschuss) Brom-benzol-Grignard in 800 cm³ Äther unter kräftigen Rühren eingetropft. Der Grignard-Komplex fällt als roter Niederschlag aus. Die Reaktionsmischung wird danach noch 1 Stde. unter Rückfluss erhitzt und anschliessend in üblicher Weise aufbereitet. Schmp. unscharf bei 111° (aus Methanol) Ausbeute: 70%.

20 g des gewonnenen Dicarbinols werden in 100 cm³ Chloroform gelöst und die Lösung unter Rühren zu 500 cm³ Chloroform und 20 g Phosphor-tribromid (Überschuss) bei 35° getropft. Darauf erwärmt man 2 Stdn. auf 60°. Die überschüssige Menge PBr_3 wird durch Wasser zersetzt. Nach Reinigung der Chloroform-Lösung destilliert man das Lösungsmittel ab; dabei fällt das Dibromid III kristallin aus.

Blassgelbe Nadeln, Schmp. 85° (aus Ligroin). Ausbeute: 80%.

(Gef.: C, 60·8; H, 4·5. $C_{23}H_{20}Br_2$ entspr.: C, 60·6; H, 4·4).

Bromabspaltung in Dimethyl-formamid. 10 g des Dibromids werden in 100 cm³ Dimethyl-formamid gelöst und innerhalb 7 Stdn. bei 40° zu 200 cm³ Dimethyl-formamid und 3 g Zinkstaub unter kräftigem Rühren eingetropft. Darauf verdünnt man zur Isolierung des Reaktionsproduktes nach Abtrennung vom überschüssigem Zink in 1 L Wasser, 5 cm³ HCl sowie 100 cm³ Äther und schüttelt anschliessend mehrfach mit Äther aus. Der Extrakt weist anfangs eine intensiv blau-grüne Fluoreszens auf, die jedoch nach der Reinigung des Extraktes mit Wasser innerhalb kurzer Zeit verschwindet.

Zur Isolation des gebildeten 1,3-*Diphenyl-2,2-dimethyl-indanol*-1 (V) wird der Äther abdestilliert, wobei ein farbloses kristallines Produkt ausfällt, dessen Zusammensetzung des Carbinols V entspricht: Schmp.: 180° (aus Methanol). Ausbeute: 75%.

Gef.: C, 87·8, 88·0; H, 7·4, 7·4. $C_{23}H_{22}O$ entspr.: C, 87·9; H, 7·1).

[17] W. Wislicenus, *Liebigs Ann.* **252**, 86 (1889).

(10) *Addition mit Maleinsäure-anhydrid. Bildung von* 1,4-*Diphenyl*-1,4-*endo* (*dimethyl*) *methylen-tetralin*-2,3-*dicarbonsäure-anhydrid* (VI)

Die Ausführung der Addition erfolgt in derselben Weise wie unter (3) beschrieben. Die bei der Aufbereitung anfallende ätherische Lösung wird eingeengt und der Rückstand in Ligroin aufgenommen. Nach Anreiben in Essigester fällt das Addukt aus. Schmp.: 344°. Ausbeute: 78%.

(Gef.: C, 82·0, 82·0; H, 5·4, 5·4. $C_{27}H_{20}O_3$ entspr.: C, 82·6; H, 5·1).

(11) *Brom-abspaltung mit Zink-amalgam. Bildung von* 1,3-*Diphenyl*-2,2-*dimethyl-iso-inden* (IV)

Unter kräftigem Rühren wird 100 g reines Quecksilber, 120 cm³ Toluol, 8 g Zink und 10 g Dibromid in Stickstoff auf 100° erhitzt, wobei sich zunächst das Zink in Quecksilber löst. Durch das Turbinieren in Toluol wird bald aus dem Amalgam Zink-durch seine extrem hohe Dispersion stark aktiviert-abgeschieden, welches aus dem Dibromid das Halogen abspaltet. Nach 10 Stdn. wird mit 2 g A-Kohle geschüttelt und über Kieselgur filtriert. Man zieht das Lösungsmittel unter Luftausschluss ab und destilliert den Kohlenwasserstoff IV i. Hochvak. Dabei erhält man ein hochviskoses gelbes Öl mit starker grünblauer Fluoreszens. Sdp. 8×10^{-4}: 145°. Ausbeute: 90%.

Nach mehrtägiger Aufbewahrung unter Luftabschluss polymeriert IV zu einem farblosen amorphen Pulver, welches in Äther unlöslich ist.

(Gef.: C, 93·4, 93·5; H, 6·7, 6·7. $(C_{23}H_{20})_x$ entspr.: C, 93·2; H, 6·8).

In Gegenwart von Luft bildet sich ein Produkt der Zusammensetzung $C_{23}H_{20}O$. Schmp.: 68°

Addition von IV *an Maleinsäure-anhydrid* (VI). 3 g des Kohlenwasserstoffes IV und 1·5 g Maleinsäure-anhydrid werden in 15 cm³ Benzol 8 Stdn. auf ca. 55° erhitzt. Beim Abkühlen fällt das Addukt vom Schmp. 344° kristallin aus. Ausbeute 98%. (Die Addition erfolgt auch innerhalb 30 Stdn. bei 25°). Der Mischschmelzpunkt mit dem unter (10) beschriebenen Addukt ergibt keine Depression.

Die Untersuchung des U.V.-Spektrums von VI weist auf isolierte Phenyl-gruppen hin, was einer Addition aus der Isoform entspricht.

(12) *Darstellung des* 1,2,2,3-*Tetramethyl*-1,3-*dibrom-indan*

Ausgehend vom 2,2-Dimethyl-indandion-1,3[17] wird durch eine Grignard-Reaktion mit Methylbromid das Tetramethyl-indandiol erhalten, welches mit Phosphor-tribromid umgesetzt das gewünschte Dibromid ergibt. Seine *Bromabspaltung* wird wieder nach dem Verdünnungsprinzip mit Zinkstaub in Dimethyl-formamid in beschriebener Weise durchgeführt. Als Reaktionsprodukt lässt sich nur bromfreies Polymerisat isolieren.

(13) *Darstellung des* 2,2-*Dimethyl*-1,3-*dibrom-indan*

Dimethyl-indandion[17] wird in Äther mit $LiAlH_4$ (10% Überschuss) unter üblichen Bedingungen zum 2,2-Dimethyl-indan-diol-1,3 reduziert und das Dicarbinol in der unter (9) beschriebenen Methode mit Phosphortribromid in Chloroform umgesetzt.

Der nach Einengen des Lösungsmittels verbleibende Rückstand ist i. Vak. destillierbar.

Farbloses Öl. $Sdp._{0,5}$: 112°.

(Gef.: C, 43·4, 43·7; H, 4·2, 4·2. $C_{11}H_{12}Br_2$ entspr.: C, 43·4; H, 4·0).

Brom-Abspaltung. Hier wird wieder dieselbe Methode wie unter (2) beschrieben angewendet. Die glatt verlaufende Reaktion ergibt bromfreies Polymerisat.

(14) *Addition mit Maleinsäure-anhydrid. Bildung von* 1,4-*Dimethyl*-1,4-*endomethylen-tetralin*-2,3-*dicarbonsäure-anhydrid* (VII)

Reaktion mit 20 g Maleinsäure-anhydrid und 25 g Dibromid wie unter (3) angegeben. Das isolierte Addukt VII wird aus Essigester kristallisiert.

Schmp. 114°. Ausbeute: 75%.

(Gef.: C, 74·3, 74·6; H, 6·0, 6·0. $C_{15}H_{14}O_3$ entspr.: C, 74·4; H, 5·8).

(15) *Brom-Abspaltung in Essigsäure*

15 g Dibromid werden in 100 cm³ Eisessig (über $KMnO_4$ destilliert) gelöst und die Lösung innerhalb 5 Stdn. zu 300 cm³ Eisessig und 3 g Zinkstaub bei 30° unter Rühren eingetropft. Pro Stunde erfolgt eine weitere Zugabe von je 1 g Zinkstaub. Die unter (1) beschriebene Aufbereitung ergibt

einen öligen Rückstand aus dem man durch Vak.-Destillation das 1-*Acetoxy*-2,2-*dimethyl-indan* (VIII) ($Sdp._{0.5}$: 74°) in 35% Ausbeute gewinnt.

(Gef.: C, 76·5, 76·4; H, 8·0, 7·9. $C_{13}H_{16}O_2$ entspr.: C, 76·4; H, 7·9).

(16) *Darstellung des* 1,3-*Dibrom-indan*

Das 1,3-Indandion[15] (50 g) wird in 100 cm³ Tetrahydro-furan (wasserfrei durch Natrium) gelöst und diese Lösung unter Rühren bei 10° zu der äquivalenten Menge (+15% Überschuss) $LiAlH_4$ in 1 L Tetrahydro-furan innerhalb drei Stdn. eingetropft. Danch lässt man noch 4 Stdn. bei 20° weiterrühren. Der LiAl-Komplex wird in üblicher Weise hydrolisiert und das anfallende Diol als Kristallisat isoliert.

Zur Gewinnung des Dibromids wird das 1,3-Indandiol wieder mit Phosphortribromid in der unter (9) beschriebenen Weise umgesetzt.

Schmp.: 110° (aus Ligroin).

(Gef.: C, 39·2, 39·2; H, 3·3, 3·1. $C_9H_8Br_2$ entspr.: C, 39·2; H, 2·9).

(17) *Brom-Abspaltung*

20 g des Dibromids werden in 80 cm³ Benzol (wasserfrei) gelöst und bei 40° zu 100 g 8-proz. Zinkamalgam in 120 cm³ Benzol unter kräftigem Rühren eingetropft. Nach 5 Stdn. schüttelt man zur Abtrennung des feindispersen anorganischen Niederschlages mit A-Kohle und nutscht über Kieselgur ab. Aus dem farblosen Filtrat zieht man das Lösungsmittel langsam über eine Kolonne ab und reinigt den Rückstand durch Vakuumdestillation über Natrium. Der farblose (ungesättigte) Kohlenwasserstoff erweist sich als Inden. Der Rückstand besteht aus Polymerisat.

(Gef.: C, 92·3, 92·0; H, 6·9, 7·1. Ber. für C_9H_8: C, 93·1; H, 6·9).

Eine zusätzliche Identifikation erfolgte durch Vergleich des Brechungsindexes.

(18) *Addition mit Maleinsäure-anhydrid*

Die Reaktion wird wie unter (3) beschrieben mit 25 g Maleinsäure-anhydrid und 10 g Dibromid durchgeführt.

Das gewonnene Addukt-1,4-Endomethylen-tetralin-2,3-dicarbonsäure-anhydrid (X) wird aus Ligroin-Essigester umkristallisiert.

Schmp. 187°. Ausbeute: 47%.

(Gef.: C, 72·8, 72·9; H, 4·9, 4·9. Ber. für $C_{13}H_{10}O_3$: C, 72·9; H, 4·7).

Die Aufbereitung des öligen Rückstandes ergibt neben wenig bromfreiem Polymerisat in etwa 40% Ausbeute Inden.

Der Mischschmelzpunkt von X mit einem Präparat anderer Herkunft (Inden u. Maleinsäure-anhydrid auf 180° im Autoklaven erhitzt) ergibt keine Schmelzpunkt-depression. Ihre Spektren stimmen ebenfalls überein.

(19) *Addition mit Acrylsäure-methylester. Bildung von* 1,4-*Endomethylen-tetralin*-2-*carbonsäure-methylester* (XI)

Mit demselben Verfahren wie unter (6) beschrieben, werden 10 g des Dibromids und 30 g Acrylsäure-ester reagiert und das Addukt in üblicher Weise isoliert. Bei der Destillation gewinnt man neben überschüssigem Acrylsäure-ester Inden in etwa 60% Ausbeute sowie als letzte Fraktion das Addukt XI als blassgelbes Öl von $Sdp._{0.15}$: 59°.

(Gef.: C, 76·4, 76·6; H, 7·1, 7·1. $C_{13}H_{14}O_2$ entspr.: C, 76·4; H, 7·9).

Das Spektrum des gesättigten Adduktes weist analog X auf einen Benzol-Kern hin, was einer Addition aus der Isoform des Indens entspricht.

[15] W. O. Teeters, *J. Amer. Chem. Soc.* **55**, 3026 (1933).

Tetrahedron, 1961, Vol. 14, pp. 201 to 207. Pergamon Press Ltd. Printed in Northern Ireland

ACTION OF MANGANESE DIOXIDE ON CARBOHYDRATES—I

SOME DISACCHARIDES

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Abstract—Manganese dioxide degrades 1 → 3, 1 → 4 and 1 → 6 linked hexose disaccharides to, *inter alia*, 1 → 2, 1 → 3 and 1 → 5 linked hexosyl-pentoses, respectively. The yields (18–31 per cent) compare favourably with those recorded for other degradations. The methods which have been worked out for the isolation of these products are experimentally straightforward, and should be generally applicable to mixtures obtained by oxidation of 3-, 4- and 6-substituted hexoses with manganese dioxide.

Previous studies[1] have shown that the principal pathway of oxidation for aldohexoses with manganese dioxide involves elimination of C1 to give the corresponding aldopentoses; some acidic products are also formed. Tetroses are probably produced from the pentoses, but they do not accumulate, being rapidly oxidized further to yield acid products. Similarly, hexosyl-hexoses give hexosyl-pentoses, with no accumulation of hexosyl-tetroses in those cases (1 → 4 and 1 → 6 linked disaccharides) where further oxidation is possible.

The direct conversion of hexose to pentose is not a common oxidation pathway of sugars, although it can be achieved using glycol cleavage reagents,[2,3] especially lead tetra-acetate. This oxidant can be used with unsubstituted hexoses,[4] when accompanying formation of tetrose necessitates chromatographic isolation of the pentose; yields vary widely with different hexoses, but are generally in the range 15–35 per cent. With a suitably substituted hexose, the yield of pentose is quantitative.[3] Hexosyl-pentoses have not been prepared by this method since, except for 1 → 3 linked disaccharides, hexosyl-tetroses are also produced.[5] Standard methods for shortening the carbon-chain of a sugar, such as the Ruff[6] or Wohl–Zemplén[7] degradations, and glycal oxidation[8] involve two or more stages, with isolation of intermediates and a consequent lowering of overall yields. Recently,[9] D-glucose has been degraded to D-arabinose in a two-stage, but single batch oxidation with hypochlorite. Because of experimental simplicity, oxidation with manganese dioxide appeared to be an attractive method for obtaining hexosyl-, O-methyl-, and deoxy-pentoses from the appropriate hexose

[1] J. L. Bose, A. B. Foster, M. Stacey and J. M. Webber, *Nature, Lond.* **184,** 1301 (1959).
[2] A. S. Perlin, *J. Amer. Chem. Soc.* **76,** 2595 (1954).
[3] J. Fried and D. E. Walz, *J. Amer. Chem. Soc.* **74,** 5468 (1952).
[4] A. S. Perlin and C. Brice, *Canad. J. Chem.* **34,** 541 (1956); A. S. Perlin, *Adv. Carbohyd. Chem.* **14,** 9 (1959).
[5] A. J. Charlson, P. A. J. Gorin and A. S. Perlin, *Canad. J. Chem.* **34,** 1811 (1956).
[6] H. G. Fletcher, Jr., H. W. Diehl and C. S. Hudson, *J. Amer. Chem. Soc.* **72,** 4546 (1950).
[7] G. Zemplén, *Ber. Dtsch. Chem. Ges.* **60,** 1555 (1927).
[8] G. E. Felton and W. Freudenberg, *J. Amer. Chem. Soc.* **57,** 1637 (1935); A. M. Gakhokidze, *J. Gen. Chem. U.S.S.R.*) **18,** 60 (1948); *Chem. Abstr.* **42,** 4948 (1948).
[9] R. L. Whistler and R. Schweiger, *J. Amer. Chem. Soc.* **81,** 5190 (1959).

derivatives. The method should be especially applicable to hexoses having a substituent or deoxy group at C3, since further oxidation of pentose products would be minimized by the absence of a C2 hydroxyl group. The oxidation of a series of model compounds was therefore examined.

The manganese dioxide used throughout was prepared from manganese sulphate and potassium permanganate under alkaline conditions.[10] Although this oxide repeatedly gave an alkaline (pH ca. 10) extract with water, it caused oxidation patterns qualitatively similar to those of the product obtained by decomposition of manganese carbonate at 250° (neutral aqueous extract), and moreover, was a better oxidant under standard conditions. Oxidations were usually performed with equal weights of disaccharide and oxidant, in water for 1 hr at 100°. In oxidations carried out at 50°, acid formation was significantly reduced. After removal of cations from an oxidation mixture, the acidic products were removed using a strongly basic anion exchanger.[11]

It soon became clear that even a large excess of manganese dioxide did not completely oxidise an aldohexose, so that an efficient fractionation procedure was required if the method was to be of preparative value. With 1 → 3 and 1 → 4 linked hexosyl-glucoses, the principal oxidation products were hexosyl-arabinoses, linked 1 → 2, and 1 → 3, respectively. In both cases, the hexosyl-glucose and hexosyl-arabinose had markedly different paper electrophoretic mobilities (M_G values) in borate buffer (pH 10)[12], and were therefore favourable mixtures for the application of borate-charcoal chromatography, a method which makes use of the reduced affinity of sugar-borate complexes for charcoal. The method was developed[13] with mixtures of melibiose and maltose, and isomaltose and maltose, but its application to mixtures containing alkali-sensitive,[14] 1 → 3 linked disaccharides, such as laminaribiose or nigerose, has not been reported. These disaccharides are degraded in solution at pH 10, but are stable while adsorbed on paper during electrophoresis in alkaline buffers. It has now been found that they are similarly stabilized whilst adsorbed on charcoal in the presence of borate at pH 10. Oxidation of maltose with manganese dioxide at 100° gave neutral products (69 per cent) comprizing arabinose, glucose, maltose (M_G 0·34) and 3-O-α-D-glucopyranosyl-D-arabinose (Compound A, M_G 0·56); this mixture was fractionated by charcoal-borate chromatography. Immediate neutralization of the column eluate prevented decomposition of Compound A, which had been eluted from the column immediately following the monosaccharides, with some overlapping of components (Fig. 1); elution of maltose did not commence until removal of Compound A was complete. Compound A was easily freed from inorganic material and monosaccharides by charcoal column chromatography,[15] and hence was recovered completely (18 per cent overall yield) from the reaction mixture. The disaccharide, which was very hydroscopic and failed to yield a crystalline heptaacetate, gave glucose and arabinose (chromatographic detection) on acidic hydrolysis. The reduced disaccharide, which was also very hygroscopic, gave glucose and arabitol on acidic hydrolysis, and a periodate oxidation pattern which agreed with that for a 3-O-D-glucopyranosyl-D-arabitol (I). The initial, very rapid uptake of periodate by a disaccharide alcohol

[10] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952).
[11] G. Machell, *J. Chem. Soc.* 3389 (1957).
[12] A. B. Foster, *J. Chem. Soc.* 982 (1953).
[13] S. A. Barker, E. J. Bourne and O. Theander, *J. Chem. Soc.* 4276 (1955).
[14] W. M. Corbett and J. Kenner, *J. Chem. Soc.* 3274 (1954).
[15] R. L. Whistler and D. F. Durso, *J. Amer. Chem. Soc.* **72**, 677 (1950).

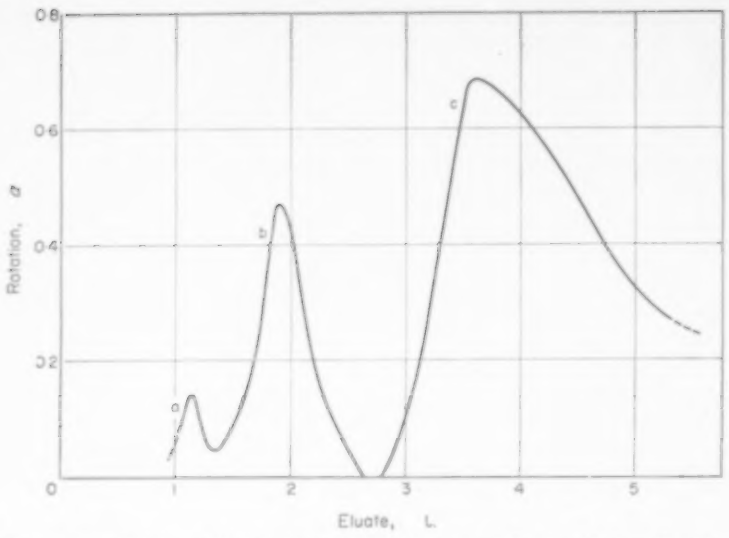
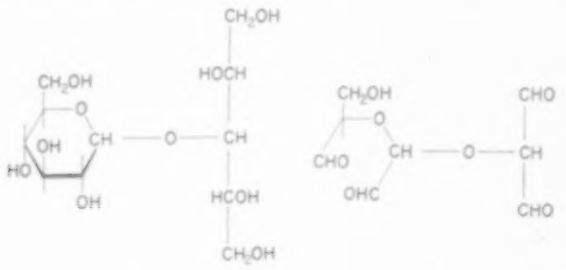


FIG. 1. Borate-charcoal fractionation of neutral products from oxidation of maltose with manganese dioxide.
(a) monosaccharides, (b) 3-O-α-D-glucopyranosyl-D-arabinose, (c) maltose.

results from attack of the acyclic moiety. With the glucosyl-arabitol, the accompanying release of 2 mole of formaldehyde (with an uptake of less than 3 mole of periodate) reveals a 1 → 3 glycosidic linkage; other glucosyl-arabitols would give only 1 mole of formaldehyde at this stage of oxidation. The slower oxidation of the cyclic moiety



I II

would give II which would be subject to overoxidation through its malondialdehyde group.[16]

The borate-charcoal method of fractionation is applicable to oxidation mixtures obtained from 1 → 3 linked hexosyl-glucoses, and it is the method of choice if recovery of unoxidized starting-material is desirable. However, the alkali-sensitivity of 1 → 3 linked disaccharides[14] permits a simpler approach in which the unoxidized substrate is selectively degraded. Thus, when the neutral products from a laminaribiose oxidation were treated with saturated lime-water, the residual laminaribiose was completely destroyed giving monosaccharide and acidic components, while the principal oxidation product, 2-O-β-D-glucopyranosyl-D-arabinose, was essentially

[16] J. L. Bose, A. B. Foster and R. W. Stephens, *J. Chem. Soc.* 3314 (1959) and references cited therein.

unaffected. Fractionation of the mixture on a charcoal column then furnished the glucosyl-arabinose in an overall yield of 31 per cent. The glucosyl-arabinose was identified by conversion to known 1,3,5-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-D-arabinose.[17] Confirmatory evidence for the 1 → 2 linkage was provided by the periodate oxidation pattern of the reduced disaccharide which consumed 3·8 mole of the oxidant with release of 1·8 mole of formic acid and 0·9 mole of formaldehyde. The theoretical values for 2-O-β-D-glucopyranosyl-D-arabitol are 4, 2, and 1, respectively.

The M_G values of 1 → 6 linked hexosyl-glucoses and their 1 → 5 linked hexosyl-arabinose oxidation products are not appreciably different, so that borate-charcoal chromatography is not feasible. Moreover, a 1 → 6 linked disaccharide cannot be selectively destroyed with alkali; alternative methods of fractionation were therefore

Table 1. Acidic products from oxidation of melibiose

Acid	Reference acid	M_{GA}	Galactosyl-aldonic acid (M_{GA})
2C	glycollic	1·77	
3C	glyceric	1·54	0·88
4C	erythronic	1·27	0·67
5C	arabonic	1·09	0·47
6C	gluconic	1·00	0·42

sought. The neutral products from a melibiose oxidation were fractionated on a charcoal column (gradient elution) to give melibiose (22 per cent overall recovery), and a mixture (33 per cent) containing melibiose and a galactosyl-arabinose; all fractions containing the galactosyl-arabinose also contained melibiose. Homogeneous galactosyl-arabinose (21 per cent overall yield) was obtained from this mixture in a small-scale (50 mg) fractionation using thick-paper chromatography. Although this disaccharide was not rigorously identified, it gave galactose and arabinose on acidic hydrolysis and, by analogy with the preceding oxidations, must be 5-O-α-D-galactopyranosyl-D-arabinose.

The procedures evolved for fractionation of mixtures obtained by oxidation of laminaribiose and maltose are straightforward, and should be applicable to a range of 3- and 4-substituted hexoses. Complete fractionation of the oxidation mixture from the 1 → 6 linked disaccharide was less easily achieved. Since the possible variations in oxidation conditions were not exhaustively examined, the recorded yields (18–31 per cent) of oxidation products cannot be considered as maximal; even so, they compare favourably with those obtained by other degradation methods.

The formation of acids during oxidation of disaccharides with manganese dioxide was greater than had previously[1] been supposed, for example, at 100°, the weight of acidic products was 18 per cent of that of the maltose substrate. Oxidation of melibiose gave the series of aldonic and galactosyl-aldonic acids listed in Table 1. The latter acids were identified by hydrolysis, after removal of aldonic acids by charcoal column chromatography. With maltose and melibiose, the principal acidic products were the corresponding glycosyl-tetronic and glycosyl-pentonic acids.

[17] B. Weissmann and K. Meyer, *J. Amer. Chem. Soc.* **76**, 1753 (1954).

EXPERIMENTAL

Wherever possible, optical rotations were measured in 2 dm tubes. Paper chromatography was performed on Whatman No. 1 paper by downward irrigation with the organic phase of butanol–ethanol–water (4:1:5). Paper electrophoresis was carried out on Whatman No. 3 paper using the enclosed strip technique,[18] with borate (pH 10),[19] or acetate (pH 5) buffers. Detection was effected with aniline hydrogen phthalate[20] or silver nitrate.[21] The mobilities of acid products in acetate buffer are expressed as M_{GA} values (GA = gluconic acid). Charcoal/Celite columns were prepared from an acid-treated[22] mixture containing equal parts of B.D.H. activated charcoal and Celite No. 545.

Pyrex glass vessels and stirring rods were used in all oxidations in order to avoid the alkali-induced side reactions which result from the use of soda-glass. Manganese dioxide was prepared from manganese sulphate and potassium permanganate under alkaline conditions.[19]

Oxidation of maltose

Manganese dioxide (12·3 g) was added to a solution of maltose (12·3 g) in water (370 ml) at 95–100° and the mixture was stirred vigorously during 1 hr at the same temp. The cooled and filtered solution was passed through a column of Amberlite IR 120 resin (H^+ form; 100 ml) and dried in the frozen state. A solution of the residue (10·7 g) in water (300 ml) was stirred overnight with Deacidite FF resin (CO_3^{2-} form, 100 ml), and the mixture was then transferred to a column containing the same resin (50 ml). The combined resins were washed with water (3 l.), and the total eluate was concentrated to give a residue (8·5 g) which was free from acid products (electrophoresis in acetate buffer).

After being washed with more water (4 l.), the resin column was eluted with 4% aqueous ammonium carbonate (300 ml). The eluate was concentrated at 40° (bath)/12–15 mm to ca. 20 ml and stirred with Amberlite IR 120 (H^+ form; 20 ml). When effervescence had ceased, the mixture was transferred to a column containing an equal volume of the same resin, the combined resins were washed with water (100 ml), and the total eluate was dried in the frozen state. Paper electrophoresis showed the residue (2·2 g) to contain hexonic (M_{GA} 1·0), pentonic (1·18), and tetronic (1·48) acids, as well as glucosyl-pentonic (0·62) and glucosyl-tetronic (0·43) acids; the last of these acids was the principal component.

Paper chromatographic and electrophoretic analyses of the neutral residue revealed arabinose, glucose, maltose (R_G 0·37, M_G 0·34) and Compound A (R_G 0·53, M_G 0·56). A solution of this mixture (8·5 g) in water (85 ml) was introduced on to a charcoal/Celite column (42 × 5·5 cm) which had been washed with borate buffer (pH 10, ca. 3·6 l.),[19] until the pH values of the solutions entering and leaving the column were the same, and then with water (100 ml). After the material had been washed on to the column with water (100 ml), elution was commenced using ethanolic borate buffer and the gradient technique;[22] the ethanol concentration was increased at a rate of 1·25% per litre. The eluate was collected in 50 ml fractions which were siphoned into tubes containing sufficient acetic acid (0·35 ml, 90%) to lower the pH of the solution to ca. 6. The fractions were analysed polarimetrically (Fig. 1), and by paper electrophoresis (borate buffer), which revealed that peaks a, b and c could be attributed to monosaccharides (mainly glucose), Compound A, and maltose, respectively. The first few fractions containing Compound A were contaminated with traces of glucose; there was no overlapping of disaccharides.

The fractions (24–51) containing Compound A were concentrated at 40° (bath)/12–15 mm to 600 ml (pH ca. 6) and introduced on to a charcoal/Celite column (16 × 3·5 cm) which was then washed with water (500 ml) to remove inorganic material and glucose. Elution with 5% aqueous ethanol gave chromatographically homogeneous Compound A (2·02 g; 18%), $[\alpha]_D$ + 47·1° (*c* 4·04 in H_2O). The product could be crystallized from aqueous ethanol, but was so hygroscopic that the m.p. could not be determined. Acetylation gave a syrup which could not be crystallized.

Characterization of compound A.

(a) *Acidic hydrolysis.* A solution of Compound A (10 mg) in N HCl (2 ml) was heated at 95–100° for 2 hr, then cooled, diluted with water (3 ml), neutralized with methyl di-n-octylamine,[23] and

[18] A. B. Foster, *Chem. & Ind.* 1050 (1952).
[19] A. B. Foster, P. A. Newton-Hearn and M. Stacey, *J. Chem. Soc.* 30 (1956).
[20] S. M. Partridge, *Nature, Lond.* **164,** 443 (1949).
[21] W. E. Trevelyan, D. P. Proctor and J. S. Harrison, *Nature, Lond.* **166,** 444 (1950).
[22] B. Lindberg and B. Wickberg, *Acta Chem. Scand.* **8,** 569 (1954).
[23] E. Lester Smith and J. E. Page, *J. Soc. Chem. Ind.* **67,** 48 (1948).

concentrated. Chromatographic examination of the residue revealed a mixture of glucose and arabinose.

(b) *Reduction with sodium borohydride*. A solution of sodium borohydride (0·6 g) in water (20 ml) was added to a solution of Compound A (1·0 g) in water (20 ml). After 3 hr, when α_D was constant, the solution was acidified with acetic acid, neutralized (pH 8) with sodium hydroxide, and introduced on to a charcoal/Celite column (8 × 1·8 cm) which was then washed with water (100 ml). Elution with 15% aqueous ethanol gave a chromatographically homogeneous (R_G 0·61, M_G 0·54), non-reducing residue (0·94 g) which was crystallized from aqueous ethanol. The colourless crystals which had $[\alpha]_D$ + 113° (*c* 1·48 in H_2O) were very hygroscopic and the m.p. could not be determined. Hydrolysis of the material as described in (a) gave a mixture of glucose and arabitol.

(c) *Periodate oxidation of reduced compound* A. A solution of the reduced product (100 mg) in water (10 ml) was treated with 2·8% sodium metaperiodate solution (50 ml), and the volume was rapidly adjusted to 100 ml. The consumption of oxidant was followed by the standard method;[24] formic acid liberation was determined, after destruction of excess periodate with ethylene glycol, by direct titration with 0·01N NaOH, and formaldehyde by the chromotropic acid method.[25] The following results were obtained:

Time (hr)	0·07	0·16	0·25	0·33	1·0	1·5	2·5	4·0	5·5	20	44	92
Oxidant consumption (moles)	2·82	3·48	—	4·66	5·82	6·09	6·26	6·66	7·02	7·14	7·52	7·85
Acidity, as formic acid (moles)	—	—	0·79	—	1·75	—	—	—	3·47	4·05	4·44*	—
Formaldehyde liberation (moles)	2·0	—	2·1	—	2·1	—	—	2·1	—	—	—	—

* 4·94 moles by back titration

Oxidation of laminaribiose

A solution of laminaribiose[26] (1 g) in water (30 ml) was stirred with manganese dioxide (1 g) for 1 hr at 50°, and then processed as in the maltose oxidation. Chromatographic examination of the neutral residue (0·98 g) revealed arabinose, glucose, laminaribiose (R_G 0·48, M_G 0·66) and Compound B (R_G 0·51, M_G 0·33). The solution obtained by dropwise addition of water (ca. 5 ml) to a mixture of the neutral products (0·895 g) and saturated lime-water (160 ml) was freed from oxygen by passage of nitrogen gas for 15 min. After storage at 25° for 30 hr, the solution was passed through Amberlite IR-120 (H^+ form, ca. 70 ml) and concentrated to yield a solid residue (0·89 g). Chromatographic and electrophoretic analyses showed that Compound B was largely unaffected, and that complete destruction of laminaribiose had occurred with formation of glucose, fructose, mannose and acidic components.

A solution of this product in water (10 ml) was introduced on to a charcoal/Celite column (13 × 3·5 cm) which was then washed with water (1550 ml) to remove acidic and monosaccharide components; elution of Compound B, commenced by the water, was continued using an aqueous-ethanol gradient (1·6% per litre). Concentration of the aqueous-ethanol eluate (1750 ml) gave chromatographically-homogeneous Compound B (0·28 g; 31%) which had $[\alpha]_D$ −46·4° (*c* 5·6 in H_2O, 1 dm tube).

Characterization of compound B

(a) Chromatographic analysis of a neutralized (methyl di-n-octylamine) hydrolysate (N HCl, 95–100°, 2 hr) revealed glucose and arabinose. A similar hydrolysis of the reduced (sodium borohydride) Compound B gave a mixture of glucose and arabitol. Oxidation of reduced Compound B with an excess (12·5 moles) of 0·43% sodium metaperiodate gave the following results:

Time (hr)	0·33	0·66	1·5	3·0	5·0	20
Oxidant consumption (moles)	2·2	2·5	2·8	3·2	3·9	3·8
Formaldehyde liberation (moles)	—	0·9	—	—	—	0·9

After 20 hr, acidity corresponding to 1·8 moles of formic acid had developed.

(b) Compound B (72 mg), fused sodium acetate (40 mg), and acetic anhydride (0·5 ml) were heated at 95–100° for 2·5 hr, with occasional shaking. After being cooled, the mixture was poured into

[24] E. L. Jackson, *Org. Reactions* **2**, 341 (1944).
[25] J. F. O'Dea and R. A. Gibbons, *Biochem. J.* **55**, 580 (1953).
[26] Prepared by acidic hydrolysis of insoluble laminarin, following S. Peat, W. J. Whelan and H. G. Lawley, *J. Chem. Soc.* 724 (1958).

ice-water (8 ml) and stored at 0° overnight. Decantation left a syrup which was washed with water and dried *in vacuo* (P_2O_5) to give a solid product (55 mg). Chloroform extraction of the decanted solution furnished additional syrupy material (57 mg). The crude products were separately crystallized from ethanol–light petroleum (b.p. 60–80°) to give 1,3,5-tri-O-acetyl-2-O-[2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl]-D-arabinose (14 mg, and 4 mg, respectively). In both cases, the product was obtained as colourless needles, m.p. 196·5–198°, alone, and 196–199°, in admixture with an authentic sample of the compound (m.p. 200·5–201°).[17] The infra-red spectrum of the product and that of a sample of the authentic compound were indistinguishable.

Oxidation of melibiose

A solution of melibiose (9·3 g) in water (280 ml) was stirred with manganese dioxide (9·3 g) for 1 hr at 95–100°, and then processed, as in the previous oxidations, to separate the neutral and acidic products.

(a) *Examination of acidic products.* Paper electrophoresis of this material (1·35 g) showed the series of galactosyl-aldonic acids and aldonic acids listed in Table 1.

Aqueous elution of the sodium salts of the acidic products (1 g) from a charcoal/Celite column (15 × 3·5 cm) furnished the following fractions (25 ml): IV—3C and 4C acids; V—3C to 6C acids; VI, VII—4C to 6C acids and galactosyl-aldonic acids; VIII to XI—galactosyl-aldonic acids. Hydrolysis (N HCl, 1 hr) of the material recovered from fractions VIII to XI yielded galactose and a mixture of 3C, 4C, and 5C aldonic acids.

A solution of the acidic products (0·35 g) in water (50 ml) was passed through a column (14 × 2·5 cm) of IR-4B resin (HO' form) which, after being washed with water (200 ml), was subjected to gradient (7·4% per litre) elution with aqueous formic acid. The following fractions (25 ml) were obtained: 36 to 38—galactosyl-aldonic acids; 39 to 60—galactosyl-aldonic and aldonic acids.

(b) *Fractionation of neutral products.* Paper chromatography and paper electrophoresis showed the presence of lyxose, galactose, melibiose (R_F 0·043, M_G 0·74) and Compound C (R_F 0·090, M_G 0·87).

A solution of the neutral products (5·5 g) in water was introduced on to a charcoal/Celite column (34 × 6 cm). Elution was commenced with water (2250 ml), continued with an aqueous ethanol gradient (5 l.; 0–5%), and completed with 6% aqueous ethanol (2·5 l.). Paper chromatography showed the following fractionation pattern.

Fraction (25 ml)	Components	Yield (g)
29–34	lyxose, galactose	—
35–50	galactose	0·09
59–108	melibiose	2·03
109–195	melibiose, compound C	3·01

A portion (50 mg) of the combined fractions 109–195 was further fractionated on a sheet of Whatman No. 17 paper (57 × 46 cm) by overnight irrigation with the butanol–ethanol–water (4:1:5) solvent. Chromatographically homogeneous Compound C (30 mg) was extracted from the appropriate strip with hot water.

Characterization of compound C

(a) *Acidic hydrolysis.* Chromatographic examination of a neutralized (methyl di-n-octylamine) hydrolysate (N HCl, 95–100°, 2 hr) showed the presence of galactose and arabinose.

(b) *Reduction with sodium borohydride.* A solution of the melibiose-Compound C mixture was treated with sodium borohydride and processed as described for Compound A. Paper chromatography showed melibiitol (R_G 0·36) and a second, non-reducing component (R_G 0·50). Paper electrophoresis in molybdate buffer (pH 5)[27] also revealed two components, having M_S 0·75 (melibiitol), and 0·50, respectively (M_S = mobility with respect to that of sorbitol). Reduced Compound C was thereby identified as a 5-O- or 4-O-substituted arabitol.

[27] E. J. Bourne, D. H. Hutson and H. Weigel, *J. Chem. Soc.* 35 (1961).

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THE RELATION BETWEEN THE CLAISEN REARRANGEMENT OF ALLYL ETHERS AND THEIR ELECTRONIC STRUCTURE

REARRANGEMENT OF N-ALLYLAMINES

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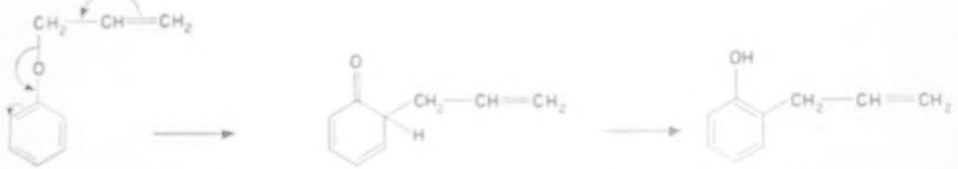
Abstract—The kinetics of a number of Claisen rearrangements have been studied and it is shown that the energy of activation of this reaction is a function of the bond orders and free valencies in the ethers undergoing rearrangement. In accordance with prediction from the derived equation, it was shown that N-allyl-1-naphthylamine rearranged smoothly and in high yield to 2-allyl-1-naphthylamine by a first order, intramolecular mechanism. This is the first recorded example of a Claisen rearrangement of an N-allyl compound. The behaviour of other ethers, whose rearrangements in the literature have been recorded as unusual or anomalous, is discussed in the light of these findings.

THE Claisen rearrangement of aromatic allyl ethers and allyl vinyl ethers has received much attention and has been extensively used in studies of the non-equivalence of bonds in aromatic compounds.[1–9] Theoretical aspects of the reaction have been in the main concerned with its mechanism. Largely due to the work of Hurd and Pollack[10], Kincaid and Tarbell,[11] Rhoads *et al.*,[12] Conroy and Firestone,[13] and Curtin and Johnson,[14] it is now clear that the rearrangement is intramolecular and of the first order



and that the mechanism is via the formation of a cyclized activated complex and an intermediate dienone.

This mechanism implies some fixation of the double bonds in the aromatic nucleus during the transition state. These earlier studies indicated that whereas in naphthalene,

[1] L. Claisen, *Ber. Dtsch. Chem. Ges.* **45**, 3157 (1912).
[2] D. S. Tarbell, *Org. Reactions* **2**, 13 (1944).
[3] L. F. Fieser and W. C. Lothrop, *J. Amer. Chem. Soc.* **57**, 1459 (1939).
[4] L. F. Fieser and W. C. Lothrop, *J. Amer. Chem. Soc.* **58**, 749 (1936).
[5] L. F. Fieser and M. N. Young, *J. Amer. Chem. Soc.* **53**, 4120 (1931).
[6] E. Ochiai and T. Nisizawa, *Ber. Dtsch. Chem. Ges.* **74**, 1402 (1941).
[7] B. Mander-Jones and W. M. Trikojus, *Proc. Roy. Soc.* N.S.W., **66**, 300 (1932).
[8] B. Mander-Jones and W. M. Trikojus, *J. Amer. Chem. Soc.* **54**, 2570 (1932).
[9] W. Baker, *J. Chem. Soc.* 1681 (1934).
[10] C. D. Hurd and M. A. Pollack, *J. Org. Chem.* **3**, 550 (1939).
[11] J. F. Kincaid and D. S. Tarbell, *J. Amer. Chem. Soc.* **61**, 3085 (1939).
[12] S. J. Rhoads, R. Raulins, and R. D. Reynolds, *J. Amer. Chem. Soc.* **75**, 2531 (1953); **76**, 3456 (1954).
[13] H. Conroy and R. A. Firestone, *J. Amer. Chem. Soc.* **75**, 2530 (1953).
[14] D. Y. Curtin and H. W. Johnson, *J. Amer. Chem. Soc.* **76**, 2276 (1954).

anthracene and phenanthrene the bonds are sufficiently stabilized to prevent the rearrangement of 2-allyl ethers occurring around the Δ^2 bond, the rearrangement of the allyl ethers of 5-hydroxyhydrindene[15] and 6-hydroxytetralin[16] is not restricted (absence of the Mills–Nixon effect) and takes place in both *ortho*-positions if they are available.

From a consideration of these facts and of the rather scanty kinetic data on the *ortho*-Claisen rearrangement, it seemed that the energy of activation of the reaction (which is a measure of the slow formation of dienone) might be used as a measure of double bond character or bond order in aromatic and aliphatic unsaturated compounds. There is kinetic data in the literature for the *ortho* rearrangement of the allyl ethers of *p*-cresol and vinyl alcohol.[17] In order to obtain sufficient data for our purposes, we have studied the kinetics of the rearrangement of several other suitably chosen aromatic ethers, using those structures for which data on bond orders was available. These were the ethers derived from 1- and 2-naphthol, 2-, 3- and 9-phenanthrol and 8-hydroxyquinoline. The details of their preparation, rearrangement and techniques used to obtain the kinetic data are described in subsequent sections below. From the data obtained (Tables 2–8), the first order rate constants (k_r) were calculated and the energy of activation for each reaction was computed from the Arrhenius equation and the entropy of activation from the Eyring equation (1), assuming the transmission coefficient to be equal to unity.[18]

$$k_r = \frac{kT}{h} \kappa \, . \, e^{(\Delta S^{\ddagger}/R)} \, e^{(-\Delta E^{\ddagger}/RT)} \qquad (1)$$

where k = Boltzmann's constant,
h is Planck's constant,
κ is the transmission coefficient,
$\Delta S^{\ddagger}$ is the entropy of activation, and
$\Delta E^{\ddagger}$ is the energy of activation.

Since it has been shown[11] that the rate of the Claisen rearrangement is only slightly affected by the nature of the solvent, we have pooled our data with the literature data, irrespective of the presence or absence of a solvent of reaction. In Table 1, the derived activation energies are compared with the bond orders of the relevant bonds in the

TABLE 1. CORRELATION OF ENERGIES AND ENTROPIES OF ACTIVATION WITH RELEVANT BOND ORDER* IN A SERIES OF CLAISEN REARRANGEMENTS

Allyl ether of:—	$\Delta E^{\ddagger}$ (Kcal)	$\Delta S^{\ddagger}$ (e.u.)	Relevant bond order
p-Cresol	33·1	−8·1	0·667
Vinyl alcohol	30·6	−7·7	1·000
1-Naphthol	26·0	−15·9	0·725
2-Naphthol	28·5	−12·0	0·725
9-Phenanthrol	21·9	−18·1	0·775
2-Phenanthrol	29·5	−11·0	0·705
3-Phenanthrol	29·5	−11·0	0·702
8-Hydroxyquinoline	29·7	−11·4	0·701

* Bond orders were obtained by L.C.A.O. approximation.[19]

[11] W. C. Lothrop, *J. Amer. Chem. Soc.* **62**, 132 (1940).
[16] S. E. Sergievskaya and A. E. Gavrilova, *Zh. Obshch. Khim.* **11**, 1027 (1941).
[17] F. W. Schuler and G. W. Murphy, *J. Amer. Chem. Soc.* **72**, 3155 (1950).
[18] H. Eyring, *J. Chem. Phys.* **3**, 107 (1935).
[19] C. A. Coulson, *Valence*. Oxford (1954).

TABLE 2. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 1-ALLYLOXYNAPHTHALENE

Temperature °C	Time (min)	Yield of 2-allyl-1-naphthol (%)	k_1
158·2	20	33·7	
	40	48·5	
	60	56·5	
	80	68·0	
	100	75·1	$2{\cdot}04 \times 10^{-4}$ sec^{-1}
172·2	5	22·4	
	10	34·2	
	15	46·3	
	20	55·5	
	30	66·5	$5{\cdot}5 \times 10^{-4}$ sec^{-1}
176·8	5	37·2	
	10	47·2	
	15	60·0	
	20	67·2	
	25	73·5	
	30	78·5	$7{\cdot}5 \times 10^{-4}$ sec^{-1}
186·1	5	42·9	
	10	61·5	
	15	73·0	
	20	82·0	
	25	86·6	$1{\cdot}30 \times 10^{-3}$ sec^{-1}
194·0	3	38·0	
	6	56·5	
	9	69·5	
	45	84·4	$2{\cdot}05 \times 10^{-3}$ sec^{-1}

aromatic compounds around which the rearrangements occur.[19] It is clear that the activation energy is not a function of the bond order alone.

That this is likely to be the case can be deduced by reasoning similar to that we have used previously for the interpretation of infra-red spectra of compounds containing intramolecular hydrogen bonds.[20] The energy of activation of the Claisen rearrangement may be considered as a function of three variables (i) the energy due to the stretching of the oxygen–carbon bond, (ii) the energy involved in the formation of the carbon–carbon bond and (iii) the resonance energy of the activated cyclic intermediate, which may be assumed to be proportional to the localization energy of the relevant bond in the aromatic compound and hence approximately proportional to its bond order. It may be further assumed that the energy due to the stretching of the oxygen–carbon bond is proportional to the carbon localization energy of the carbon atom in the aromatic compound that bears the oxygen atom, and that the energy due to the formation of the carbon–carbon bond is proportional to the carbon localization energy of the aromatic carbon atom involved in the rearrangement. In view of the parallelism

[20] S. Marcinkiewicz and J. Green, *J. Chem. Soc.* 849 (1959).

TABLE 3. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 2-ALLYLOXYNAPHTHALENE

Temperature °C	Time (min)	Yield of 1-allyl-2-naphthol (%)	k_r
158·2	20	11·0	
	40	19·5	
	60	29·4	
	80	34·2	
	100	38·0	$8{\cdot}8 \times 10^{-5}$ sec^{-1}
172·1	15	20·0	
	20	25·5	
	30	35·1	
	40	43·6	$2{\cdot}42 \times 10^{-4}$ sec^{-1}
180·0	15	33·3	
	20	39·5	
	25	46·6	
	30	53·5	
	35	61·0	
	40	66·0	$4{\cdot}45 \times 10^{-4}$ sec^{-1}
186·1	10	35·0	
	15	45·0	
	20	55·0	
	30	69·4	$6{\cdot}85 \times 10^{-4}$ sec^{-1}
194·0	5	28·0	
	10	48·5	
	15	65·1	
	60	98·7	$1{\cdot}13 \times 10^{-3}$ sec^{-1}

between free valencies and carbon localization energies, the energy of activation for the rearrangement of any allyl ether is then given by the equation:

$$\Delta E^{\ddagger} = K \cdot p_{rs} + LF_r + L'F_s + M \qquad (2)$$

where p_{rs} stands for the mobile bond order of the bond of the aromatic or vinyl compound involved in the rearrangement, F_r is the free valence of the carbon atom that forms the new carbon–carbon bond, and F_s is the free valence of the carbon atom bearing the allyloxy group. K, L, L′ and M are constants characteristic for the rearrangement of any allyl ether. Substituting the values from Table 1 in the general equation (2), a set of 8 equations is obtained, which are approximately consistent for values of K, L, L′ and M of −45, −36, −100 and 75, respectively. That the agreement is not fortuitous is indicated from a consideration of other data in the literature, which can now be discussed.

While allyl vinyl ether and allyl α-methylvinyl ether (especially the former) require temperatures of over 250° for appreciable rearrangement to take place,[17,21] allyl α-phenylvinyl ether rearranges in a few minutes[21] at temperatures below 175°, although the bond order in styrene is *less* than that in ethene. By utilizing the known values for the bond orders in styrene in equation (2), we obtain a theoretical energy of activation

[21] C. D. Hurd and M. A. Pollack, *J. Amer. Chem. Soc.* **60**, 1905 (1938).

TABLE 4. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 8-ALLYLOXYQUINOLINE

Temperature °C	Time (min)	Yield of 7-allyl-8-hydroxy quinoline (%)	k_r
158·0	85	12·4	
	110	15·6	
	140	18·8	
	170	22·4	
	195	26·0	$2{\cdot}5 \times 10^{-5}$ sec^{-1}
171·9	30	17·6	
	60	26·0	
	90	35·2	
	120	43·5	
	150	50·5	$7{\cdot}5 \times 10^{-5}$ sec^{-1}
180·6	10	8·0	
	20	17·4	
	40	30·1	
	80	47·6	
	120	64·0	$1{\cdot}42 \times 10^{-4}$ sec^{-1}
186·0	10·5	12·0	
	20	20·6	
	30	32·0	
	40	38·8	$2{\cdot}05 \times 10^{-4}$ sec^{-1}
194·0	15	30·2	
	30	48·5	
	45	63·0	
	250	98·1	$3{\cdot}70 \times 10^{-4}$ sec^{-1}

for the rearrangement of allyl α-phenylvinyl ether of 16·2 kcal. This can be compared with the value of 30·6 kcal for allyl vinyl ether itself and readily accounts for the observed rate of reaction. The fact that allyl α-methylvinyl ether rearranges more readily than allyl vinyl ether[21] may be due to hyperconjugation, which would cause a decrease in the bond order of the vinyl double bond but would increase the relevant free valencies. The determination of the energies of rearrangement of these vinyl ethers would thus make it possible to determine approximately the degree of delocalization of π electrons in propene. A further example of the importance of free valencies in the Claisen rearrangement occurs in the rearrangement of allyloxy quinones. According to equation (2), the energy of activation for the rearrangement of an allyloxy-*p*-benzoquinone would be only about 5 kcal/mole, and, although the entropy of activation for such a rearrangement might be highly negative (since Table 1 indicates that the $\Delta S^{\ddagger}$ tends to decrease as $\Delta E^{\ddagger}$ decreases), it could be expected that the reaction would be nearly complete at room temperature in a few hours. Although allyloxybenzoquinones have not been prepared, Fieser[22] prepared 2-allyloxy-1,4-naphthoquinone and indeed observed that it rearranged *within a few minutes* at 135°. Calculation shows that bond orders and free valencies in this compound are probably similar to what would exist in the hypothetical allyloxybenzoquinone.

[21] L. F. Fieser, *J. Amer. Chem. Soc.* **48**, 3201 (1926).

TABLE 5. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 9-ALLYLOXYPHENANTHRENE

Temperature °C	Time (min)	Yield of 10-allyl-9-hydroxyphenanthrene (%)	k_r
82·1	60	8·6	
	120	15·9	
	180	22·9	
	240	29·9	$2{\cdot}42 \times 10^{-5}$ sec^{-1}
100·0	40	22·2	
	60	32·0	
	90	44·6	
	120	53·8	
	180	68·4	$1{\cdot}06 \times 10^{-4}$ sec^{-1}
110·0	15	19·6	
	30	35·1	
	45	47·5	
	60	58·1	
	75	66·6	$2{\cdot}4 \times 10^{-4}$ sec^{-1}
130·2	5	25·0	
	10	43·8	
	15	57·8	
	20	68·0	$9{\cdot}6 \times 10^{-4}$ sec^{-1}

TABLE 6. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 2-ALLYLOXYPHENANTHRENE

Temperature °C	Time (min)	Yield of 1-allyl-2-hydroxyphenanthrene (%)	k_r
158·0	30	5·1	
	60	9·0	
	90	13·0	
	120	16·6	
	180	23·7	$2{\cdot}45 \times 10^{-6}$ sec^{-1}
180·6	10	8·2	
	20	15·4	
	30	22·7	
	40	30·0	
	50	34·6	$1{\cdot}44 \times 10^{-4}$ sec^{-1}
194·0	10	20·0	
	20	35·4	
	30	48·5	
	40	58·0	
	50	66·9	$3{\cdot}69 \times 10^{-4}$ sec^{-1}

TABLE 7. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 3-ALLYLOXYPHENANTHRENE

Temperature °C	Time (min)	Yield of 4-allyl-3-hydroxyphenanthrene (%)	k_r
158·0	30	4·9	
	60	8·7	
	90	12·8	
	120	16·7	
	180	24·1	$2{\cdot}56 \times 10^{-5}$ sec^{-1}
180·6	10	7·9	
	20	14·7	
	30	22·4	
	40	29·8	
	50	34·2	$1{\cdot}39 \times 10^{-4}$ sec^{-1}
194·0	10	20·5	
	20	35·6	
	30	49·0	
	40	57·8	
	50	67·0	$3{\cdot}68 \times 10^{-4}$ sec^{-1}

TABLE 8. FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF N-ALLYL-1-NAPHTHYLAMINE

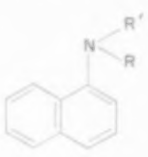
Temperature °C	Time (min)	Yield of 2-allyl-1-naphthylamine (%)	k_r
240·2	30	5·4	
	60	10·6	
	90	15·9	
	120	20·5	$3{\cdot}2 \times 10^{-5}$ sec^{-1}
258·2	10	7·0	
	20	11·0	
	30	16·0	
	40	20·9	
	50	25·0	
	60	29·7	$9{\cdot}6 \times 10^{-5}$ sec^{-1}
280·0	10	18·7	
	20	32·6	
	30	43·9	
	40	54·8	
	60	69·8	
	180	91·7	$3{\cdot}28 \times 10^{-4}$ sec^{-1}

The fact that pyrolysis of N-allylaniline gives propene and aniline instead of the expected *o*-allylaniline[23] can now be understood. The energy of the cyclic transitional state is lowest when it is coplanar with the aromatic ring. In aromatic allylamines more energy is required to bring about coplanarity than in allyl ethers, since the nitrogen atom is pyramidal. The cyclic transitional state in the rearrangement of aromatic allylamines would also lead to a more negative entropy of activation due to

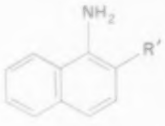
[23] F. L. Canahan and C. D. Hurd, *J. Amer. Chem. Soc.* **52**, 4586 (1930).

inhibition of the rotation of the amino hydrogen atom. Since the energy of activation for the rearrangement of allyl phenyl ether, derived by calculation from equation (2), is about 34·0 kcal and it appears that about 6 kcal is necessary to bring the nitrogen atom into the planar state,[19] the energy of activation for the hypothetical rearrangement of N-allylaniline would be about 40 kcal. The combination of high energy of activation and large negative entropy of activation would mean that the rearrangement would only take place at very high temperatures and it is therefore not surprising that at 275° only cleavage was observed,[23] since the latter reaction would occur with a positive entropy of activation.

An experimental verification would be available in the case of allylamines that correspond structurally to allyl ethers that rearrange with exceptionally low activation energies, in which case the allylamine rearrangement might be expected to occur at temperatures lower than that at which cleavage becomes important. In accordance with this hypothesis, we have prepared N-allyl-1-naphthylamine (I, R = H, R′ = $CH_2{\cdot}CH{=}CH_2$) since $\Delta E^{\ddagger}$ for the rearrangement of allyl 1-naphthyl ether is only 26·0 kcal. When this compound was heated to 280° for 3 hours, it rearranged to give 2-allyl-1-naphthylamine (II; R′ = $CH_2{\cdot}CH{=}CH_2$) in 90 per cent yield. A small



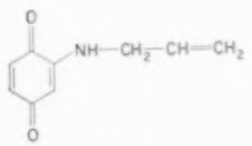
I



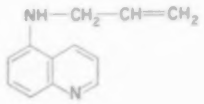
II

amount of unchanged N-allyl-1-naphthylamine remained, but cleavage, if it occurred, was so little as to be unmeasurable. This is thus the first example of a Claisen rearrangement from a nitrogen atom. The rearrangement was found to be of the first order with $\Delta E^{\ddagger} = 32{\cdot}4$ kcal (predicted 32·0 kcal) and $\Delta S^{\ddagger} = -17$ e.u.

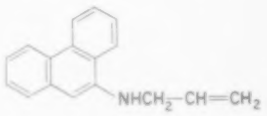
As a consequence of the theoretical treatment it should be possible to predict the pattern of rearrangement for several other interesting allylamines. Thus, 2-allylaminobenzoquinone (III) can be expected to rearrange with $\Delta E^{\ddagger} = 12$ kcal; that is, at such a rate that at room temperature it would rearrange within a few hours to give the *ortho*-substituted primary amine. 5-Allylaminoquinoline (IV) would be expected



III



IV

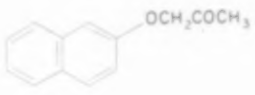


V

to rearrange with $\Delta E^{\ddagger} \approx 33$ kcal and 9-allylaminophenanthrene (V) with $\Delta E^{\ddagger} \approx 28$ kcal. It is possible that 2-allylaminopyridine (but not the 3-allylamino compound) would rearrange with $\Delta E^{\ddagger} \approx 29$ kcal. However, the calculations for this compound are complicated by the contribution of dipolar structures to the resonance hybrid, and there is thus considerable uncertainty. For similar reasons, equation (2) cannot be applied to calculations of $\Delta E^{\ddagger}$ for the rearrangement of vinylamines.

Another type of rearrangement that could take place in compounds having partly localized π electrons and high free valencies is the rearrangement of aryloxyketones. Tarbell[24] investigated the reaction of *p*-tolyloxypropanone, but found that, although a little *p*-cresol was formed by cleavage, no rearrangement took place. We have found that when 1-naphthoxypropanone (VI) and 2-naphthoxypropanone (VII) were heated

VI



VII

at 280° for 3 hours, the 2-naphthoxypropanone was largely unchanged, only a small amount of 2-naphthol being detected in the product by paper chromatography, but the 1-naphthoxypropanone decomposed almost completely, giving 1-naphthol together with some tarry material. The failure of these compounds to rearrange may be due to the very low resonance energy of the transitional state, in which the lone electron pairs on the oxygen atoms are not significantly delocalized. Nevertheless, the fact that 1-naphthyloxypropanone is much less stable to heat than the 2-naphthyloxy compound corroborates the importance of free valence in reactions.

This theoretical treatment does not make it possible to decide whether the Claisen rearrangement involves homolytic or heterolytic fission of the oxygen–carbon and nitrogen–carbon bonds, since in alternant hydrocarbons the polarization energy of a given carbon atom is independent of the nature of the polarization postulated. However, the fact that the energy of activation of the rearrangement of 8-allyloxyquinoline is consistent with equation (2) although the electronic charges at C-7 and C-8 are not equal to unity, suggests that homolytic fission of the oxygen–carbon bond occurs. If this conclusion is correct, a suitably modified form of equation (2) could be used for a study of bond orders and free valencies in various substituted allyl radicals.

That bond orders in the allyl radical itself may play a part in determining the energy of activation of the Claisen rearrangement is in fact clear from a study of available information in the literature. For example, Tarbell and Wystrach[25] studied the pyrolysis of arylmethyl ethers of 3,5-dichloro-salicylic acid. They found that while the first stage in the pyrolysis of the benzyl and β-naphthyl methyl ethers was cleavage, followed by the formation of the corresponding arylmethyl esters, the 9-phenanthrylmethyl ether mainly rearranged to 9-methyl-10-(2-hydroxy-3,5-dichlorophenyl)-phenanthrene. It is now generally held that simultaneous breaking of the carbon–oxygen bond and formation of the carbon–carbon bond occurs in the first stage of the Claisen rearrangement. This implies that in the transitional state the π electrons in the allyl radical are delocalized and contribute to the resonance of the transitional state. When the allyl radical is an arylmethyl group, the decrease of the energy of activation due to the resonance in the transitional state is opposed by the increase of the energy due to the localization energy of the two π electrons in the arylmethyl group. When the arylmethyl group is benzyl or naphthylmethyl, this localization energy is large (30 kcal for benzene, 22 kcal for the $\Delta 1$ bond in naphthalene) and consequently the energy of activation for the hypothetical Claisen rearrangement would be higher than

[24] D. S. Tarbell, *J. Org. Chem.* **7**, 251 (1942).
[25] D. S. Tarbell and V. F. Wystrach, *J. Amer. Chem. Soc.* **65**, 2149 (1943).

the energy of the cleavage reaction. When, however, the aryl methyl group is 9-phenanthrylmethyl, the energy of localization of the Δ9 bond is only 16 kcal, and the Claisen rearrangement could be expected to take place, on condition that the energy of rearrangement of the allyl ether of 3,5-dichlorosalicyclic acid is of the order of 20 kcal or less (36 kcal being probably the maximum value for the energy of activation if an ether is to rearrange at a reasonable temperature). It is again in accordance with the requirements of theory that, in fact, Claisen and Eislib[26] noted that allyl ethers of substituted salicyclic acids rearrange with elimination of carbon dioxide *at about* 100°, which indicates an energy of activation of the same order as that of 9-allyloxyphenanthrene, i.e. about 20 kcal. The energy of activation for the rearrangement of the 9-phenanthrylmethyl ether of 3,5-dichlorosalicyclic acid cannot be calculated from equation (2), since there are additional complications due to hydrogen bonding between the carboxy and allyloxy groups. Nevertheless this energy of activation could be calculated empirically if data was available on the energy of activation for the rearrangement of the allyl ether and the effect of free valencies in the allyl radical on this energy. This effect could probably be determined from a series of kinetic experiments with several suitable arylmethyl ethers of a phenol or enol and a mathematical treatment similar to that used in the present study.

Preparation of ethers, amines and rearrangement products

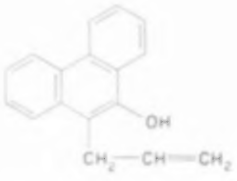
2-Allyloxynaphthalene has been described as a low-melting solid decomposing on distillation[27,28] and readily decomposing on being heated to give 1-allyl-2-naphthol.[1,27] 1-Allyloxynaphthalene also decomposed on attempted distillation[26,28,29] and its rearrangement has been described.[28] We have found that both ethers can be distilled in a short-path still under high vacuum, with only a minimal amount of rearrangement occurring. Both ethers underwent smooth rearrangement when heated under reflux in decalin for 40 minutes to give the *ortho*-substituted naphthols.

2-Allyloxy- and 3-allyloxyphenanthrene were prepared and rearranged according to Fieser and Young.[5] The compounds were found to be stable at 100° under nitrogen. In the presence of air at 100°, they turn yellow, but no rearrangement takes place. 9-Allyloxyphenanthrene was prepared by shaking the phenanthrol with allyl bromide in the presence of acetone and potassium hydroxide under nitrogen. When this ether was heated in iso-octane, under nitrogen, in a sealed tube at 156° for 3 hours it gave an oil that analysed correctly for the substituted phenanthrol (VIII). Attempts at purification through crystallization eventually gave a compound with m.p. 139° that analysed for $C_{17}H_{14}O_3$. This unexpected product liberated iodine from potassium iodide, behaved abnormally on reverse-phase paper chromatography, and had an infra-red spectrum that exhibited a very typical sharp band close to 3·0 mμ due to vibrations of an O—O—H (hydroperoxide) group.[30] These properties are consistent with it being the hydroperoxide (IX) formed through the unusually facile oxidation of 10-allyl-9-phenanthrol by atmospheric oxygen.* Fieser and Young[5] commented on the instability of 9-phenanthrol derivatives and the ease with which they can be oxidized by

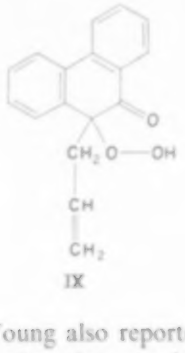
* The structure of this compound was elucidated with the help of Dr. D. McHale of these laboratories, to whom we express our thanks.

[26] L. Claisen and O. Eislib, *Monatsh.* **401**, 21 (1913).
[27] C. A. Hurd and L. Schmerling, *J. Amer. Chem. Soc.* **59**, 107 (1937).
[28] V. H. Dermer and O. C. Dermer, *J. Org. Chem.* **3**, 285 (1938).
[29] V. L. Tweedie and M. Cuscurida, *J. Amer. Chem. Soc.* **79**, 5463 (1957).
[30] O. D. Shreve, N. R. Heether, H. B. Knight and D. Swern, *Analyt. Chem.* **23**, 282 (1951).

atmospheric oxygen. In the case of retinol (8-isopropyl-2-methyl-9-phenanthrol), however, they found that oxidation stopped at 9,10-quinone stage. Fieser and Young successfully rearranged the allyl ether of retinol but gave no analysis on the oily product and identified it as the crystalline acetate. Accordingly, for analytical purposes, we converted 10-allyl-9-phenanthrol immediately after the rearrangement to an acetate, on which the required analysis was obtained. The allyl substituted phenanthrol was fortunately stable enough to be determined chromatographically in the same way as



VIII



IX

the other compounds under study. Fieser and Young also reported that the allyl ethers of 2-phenanthrol and 3-phenanthrol rearranged on the water-bath so easily that they could not be purified by vacuum distillation. We found the compounds to be stable at 100°, when heated for 4 hours, and this would be expected from our kinetic studies on these compounds. It is likely that the difficulties encountered by Fieser and Young were due to oxidation rather than rearrangement.

8-Allyloxy-quinoline was prepared according to Mander-Jones and Trikojus.[7]

N-Allyl-1-naphthylamine (I; R = H, R′ = $CH_2{\cdot}CH{:}CH_2$) has been used in pharmacological studies by several workers[31] who have not, however, described the properties of the substance. A substance described as N-allyl-1-naphthylamine was prepared by Sloviter[32] by the action of allyl chloride on 1-naphthylamine, its structure being based on an iodine number and nitrogen analysis. We were unable to repeat this experiment satisfactorily and other methods of preparation were investigated.

N-*p*-Toluenesulphonyl-1-naphthylamine with allyl bromide afforded N-allyl-N-*p*-toluenesulphonyl-1-naphthylamine (I; R = $p{\cdot}CH_3{\cdot}C_6H_4{\cdot}SO_2$; R′ = $CH_2{\cdot}CH{:}CH_2$). Attempts to effect acid or alkaline hydrolysis of the sulphonamide were unsuccessful: treatment with sodium in butanol cleaved the sulphonamide to an oil which gave a crystalline hydrochloride in poor yield. This was not N-allyl-1-naphthylamine hydrochloride, but appeared from the analytical figures to be the hydrochloride of a dihydro-derivative. Infra-red evidence supported a dihydronaphthalene structure. The required allyl-naphthylamine was eventually obtained by direct allylation of 1-naphthylamine with allyl bromide in the presence of potassium carbonate. After a preliminary distillation the bases were converted into hydrochlorides and fractionally crystallized, the separation being followed by infra-red spectra. Two isomeric monoallylated naphthylamine hydrochlorides were obtained, the major product being N-allyl-1-naphthylamine. The free base had b.p. 120°/0·5 mm, compared with b.p.

[31] U.S.P. 2,381,071 (Eastman Kodak Co.); H. Endo, *Sci. Rep. Res. Inst., Tohoku Univ.* Ser. C, **7**, 351 (1957) and subsequent papers.
[32] H. A. Sloviter, *J. Amer. Chem. Soc.* **71**, 3360 (1949).

110–120°/4 mm for the material described by Sloviter. Its structure was confirmed by conversion to the *p*-toluenesulphonamide, which was identical with the product isolated from the reaction of N-*p*-toluenesulphonyl-1-naphthylamine with allyl bromide. The second product contained a primary amino-group and appeared to be a C-allylnaphthylamine hydrochloride: catalytic reduction gave the corresponding C-propylnaphthylamine hydrochloride, which formed crystalline acetyl and benzoyl derivatives. These were not the same as those derived from 4-propyl-1-naphthylamine as described by Sergievskaya and Uretskaya.[33] Catalytic reduction of N-allyl-1-naphthylamine hydrochloride gave not the n-propyl derivative but 1-naphthylamine hydrochloride, characterized as acet-α-naphthalide. A somewhat analogous cleavage of an O-allyl ether has been described by Moffett and Seay,[34] who found that 2-allyloxy-3,5-bis-n-propyl-benzamide yielded the 2-hydroxy derivative on hydrogenation.

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When N-allyl-1-naphthylamine was heated in a sealed tube at 260° for 4 hours, smooth rearrangement took place to give 2-allyl-1-naphthylamine (II; R′ = CH_2—CH=CH_2). Its structure was confirmed by conversion into the known *p*-nitrobenzoate of 2-allyl-1-naphthol. The derived hydrochloride showed no depression on mixed melting point with the foregoing C-allyl-1-naphthylamine hydrochloride and the infra-red spectra of the two compounds were identical. On catalytic reduction, it yielded 2-n-propyl-1-naphthylamine hydrochloride (II; R = n—C_3H_7) and hence the acetyl and benzoyl derivatives, all of which were identical with the products obtained from the C-allyl-1-naphthylamine obtained by direct allylation. It therefore appears that some C-allylation of 1-naphthylamine takes place in addition to N-allylation under the conditions used, since the temperature (boiling acetone) was far too low to have produced the C-allyl compound by a Claisen rearrangement.

EXPERIMENTAL

2-Allyloxynaphthalene

β-Naphthol (10·0 g), allyl bromide (8·4 g), potassium carbonate (9·6 g), and acetone (70 ml) were heated under reflux for 2 hr. The acetone was removed under red. press. and the slurry treated with aqueous N-sodium hydroxide and extracted with ether. The ether washings were washed with water, dried, and evaporated to give a light brown oil (10·2 g). A portion of the oil (5 g) in light petroleum (b.p. 40–60°) was percolated through a column of alumina (5″ × 1″, Spence type '0') and the elute evaporated to give an almost colourless oil which was distilled in a short-path still, b.p. 55–60° (bath)/10^{-2} mm (Pirani) as a colourless mobile oil (4·2 g), n_D^{21} 1·6078 (Hurd and Schmerling[25] give n_D^{25} 1·600). The picrate formed yellow needles from ethanol, m.p. 96–97° (lit,[25] m.p. 98·5–99°).

1-*Alloxynaphthalene* was similarly prepared as a colourless oil, b.p. 60° (bath)/10^{-2} mm (Pirani), n_D^{22} 1·6055 (lit,[25] n_D^{25} 1·6038). (Found: C, 84·6; H, 6·5. $C_{13}H_{12}O$ requires: C, 84·8; H, 6·6%). The picrate formed orange-yellow needles from ethanol, m.p. 99–100° (lit,[26] m.p. 100·5–101°).

1-Allyl-2-naphthol

2-Naphthylallyl ether (5·0 g) in decalin (50 ml) was heated under reflux for 40 min, cooled, diluted with ether and extracted with aqueous N-sodium hydroxide. Acidification of the extracts gave an oil which was collected and distilled, b.p. 130–134°/0·6 mm. Crystallization from light petroleum (b.p 60–80°) gave the product as colourless prisms, m.p. 56° (3·0 g) (lit,[1] m.p. 55°).

2-*Allyl-1-naphthol* similarly prepared had b.p. 114°/0·2 mm, needles from light petroleum (b.p. 40–60°), m.p. 35–36° (Found: C, 84·5; H, 6·6. Calc. for $C_{13}H_{12}O$: C, 84·8; H, 6·6%). Claisen and Eislib[25] describe the naphthol as an oil, b.p. 171°/12 mm.

[33] S. I. Sergievskaya and G. Ya Uretskaya, *Zh. Obshch. Khim.* **23**, 1522 (1953).
[34] R. B. Moffett and P. B. Seay, *J. Med. Pharm. Chem.* **2**, 213 (1960).

9-Alloxyphenanthrene

9-Phenanthrol (2 g), allyl bromide (4 ml), acetone (20 ml), and 20% aqueous potassium hydroxide (5 ml) were shaken together under nitrogen for 4 hr at room temp. The product was extracted into a 1:1 mixture of light petroleum and ether, washed several times with water followed by 20% potassium hydroxide solution and finally with water. The crude ether was dissolved in light petroleum and purified by passing it through a short column (10 × 1 cm) of Decalso F. The column was eluted with the same solvent (200 ml). Evaporation gave 9-allyloxyphenanthrene, crystallized from methanol, m.p. 67°. (Found: C, 87·0; H, 6·1. $C_{17}H_{14}O$ requires: C, 87·1; H, 6·0%). The ether was rearranged by heating in iso-octane, under nitrogen, in a sealed tube at 156° for 3 hr. The product was chromatographed on Decalso F and eluted with benzene. Crystallization from dil ethanol, then methanol, and finally light petroleum–benzene gave a *product*, m.p. 139°, which turned yellow in air. Its properties and infra-red spectrum were consistent with it being 10-*allyl*-10-*hydroperoxy*-9-*oxo*-9,10-*dihydrophenanthrene* (the hydroperoxide of 10-allyl-9-phenanthrol IX). (Found: C, 76·5; H, 5·0. $C_{17}H_{14}O_3$ requires: C, 76·8; H, 5·3%). In another preparation, the rearranged ether was analysed directly (Found: C, 87·0; H, 6·1. $C_{17}H_{14}O$ requires: C, 87·1; H, 6·0%), showing that no cleavage occurred and was converted immediately to the *acetate*, crystallized from light petroleum (b.p. 60–80°), m.p. 124–125°. (Found: C, 82·9; H, 5·5. $C_{19}H_{16}O_2$ requires: C, 82·6; H, 5·8%).

N-*Allyl*-N-*p*-*toluenesulphonyl*-1-*naphthylamine*

N-*p*-Toluenesulphonyl-1-naphthylamine[35] (17·5 g), allyl bromide (6·4 g), potassium carbonate (5·4 g) and acetone (80 ml) were refluxed for 2 hr. The *product*, isolated by addition of water, formed needles from methanol (18·0 g), m.p. 95–96° (Found: 70·8; H, 5·8; N, 4·2. $C_{20}H_{19}NO_2S$ requires: C, 71·25; H, 5·7; N, 4·2%).

N-*Allyldihydro*-1-*naphthylamine hydrochloride*

To the foregoing sulphonamide (11·2 g) and n-butanol (85 ml), heated on the steam-bath, sodium metal (7·7 g) was added in portions. After the addition was complete, the solvent was removed, and the residual oil treated with water and extracted with ether. The ether was removed and the residual oil distilled giving a main fraction of colourless oil (3·45 g), b.p. 128–138°/0·4 mm, $n_D^{20\cdot5}$ 1·5918. The non-volatile fraction solidified on cooling and after crystallization from ethanol formed needles (2·9 g), m.p. 157–159°. The identity of this solid was not established. The oil was converted into the hydrochloride with ethanolic hydrogen chloride and the *product* crystallized from ethyl acetate–methanol to give needles, m.p. 179–180° (Found: C, 71·2; H, 7·4; N, 6·2; Cl, 15·4. $C_{13}H_{16}Cl\,N$ requires: C, 70·5; H, 7·3; N, 6·3; Cl, 16·0%).

Reaction of 1-*naphthylamine with allyl bromide*

1-Naphthylamine (57·2 g), allyl bromide (48·4 g), potassium carbonate (56 g), and acetone (400 ml) were heated under reflux for 6 hr. The solid was filtered off and rejected and the filtrate evaporated and distilled under red. press. (i) b.p. 114–118°/0·5 mm, (32·3 g), $n_D^{21\cdot5}$ 1·6509; (ii) b.p. 119–124°/0·5 mm, (22·5 g) $n_D^{21\cdot5}$ 1·6460; (iii) b.p. 125–128°/0·5 mm; (10·9 g), $n_D^{21\cdot5}$ 1·6488. The fractions were all viscous pale yellow oils and after conversion into the hydrochlorides were fractionally crystallized from ethanol or ethanol–ether, the course of the separation being followed by m.p.s and infra-red spectra. The following pure fractions were isolated: 1-*naphthylamine hydrochloride* (10·2 g), m.p. 270–271°; N-*allyl*-1-*naphthylamine hydrochloride*, needles from ethanol (11·7 g), m.p. 229–230° (Found: C, 70·8, H, 6·4; N, 6·4. $C_{13}H_{14}Cl\,N$ requires: C, 71·1; H, 6·4; N, 6·4%); 2-*allyl*-1-*naphthylamine hydrochloride*, long needles from ethanol (2·2 g), m.p. 222–223°. (Found: C, 70·9; H, 6·3; N, 6·5. $C_{13}H_{14}Cl\,N$ requires: C, 71·1; H, 6·4; N, 6·4%). The remaining crude solids (33 g) were not further investigated. N-*Allyl*-1-*naphthylamine* regenerated from the hydrochloride was an almost colourless oil, b.p. 120°/0·5 mm. (Found: C, 85·0; H, 7·0; N, 7·8. $C_{13}H_{13}N$ requires: C, 85·3; H, 7·1; N, 7·65%). When treated with *p*-toluenesulphonylchloride in pyridine on the steam-bath for 15 min, N-allyl-N-*p*-toluenesulphonyl-1-naphthylamine was obtained, m.p. 96–98° not depressed on admixture with an authentic sample.

[35] O. N. Witt and G. Schmidt, *Ber. Dtsch. Chem. Ges.* **27**, 2370 (1894).

2-Propyl-1-naphthylamine hydrochloride

2-Allyl-1-naphthylamine hydrochloride (0·3 g) in ethanol (150 ml) was shaken with hydrogen and 10% palladized charcoal till uptake of gas ceased. After removal of the catalyst, concentration yielded the *product* (0·26 g) which separated from ethanol as needles, m.p. 229–230° (Found: C, 69·9; H, 7·2; N, 6·3. $C_{13}H_{16}ClN$ requires: C, 70·4; H, 7·3; N, 6·3%). The *acetyl derivative*, needles from aqueous ethanol, had m.p. 152·5–153·5° (Found: C, 79·3; H, 7·3; N, 6·2. $C_{15}H_{17}NO$ requires: C, 79·2; H, 7·5; N, 6·2%). The *benzoyl derivative* formed needles from ethanol, m.p. 183–184° (Found, C, 83·4; H, 6·4; N, 4·8. $C_{20}H_{19}NO$ requires: C, 83·1; H, 6·6; N, 4·8%).

Reduction of N-allyl-1-naphthylamine hydrochloride

(a) The hydrochloride (0·5 g) in ethanol (80 ml) was shaken with hydrogen and 10% palladized charcoal. Initial uptake was very rapid but slowed up after ca. 1 mole of hydrogen had been absorbed. Shaking was stopped after absorption of ca. 1·2 moles, the catalyst removed and the solvent evaporated. Crystallization of the residual pale yellow solid from ethanol yielded small white needles (0·16 g), m.p. 260–265°, not depressed on admixture with α-naphthylamine hydrochloride and giving an identical infra-red spectrum.

(b) In another experiment the crude hydrochloride was converted into the base and warmed with acetic anhydride. N-Acetyl-1-naphthylamine formed needles from water, m.p. 159–160° (Found: C, 77·4; H, 6·0; N, 7·6. Calc. for $C_{12}H_{11}NO$: C, 77·7; H, 6·0; N, 7·6%).

Rearrangement of N-allyl-1-naphthylamine

N-Allyl-1-naphthylamine hydrochloride (3·0 g) was converted into the base which was heated in a sealed tube at 260° for 3 hr. The pale yellow oil was distilled in a short-path still, [76–90° (bath)/8 × 10^{-3} mm (Pirani)] as a colourless viscous oil (1·76 g), $n_D^{21·5}$ 1·6497. It was converted into the hydrochloride (1·85 g), needles from ethanol, m.p. 216–218° not depressed on admixture with 2-allyl-1-naphthylamine hydrochloride prepared as described above. The free base (0·2 g) was diazotized in 5 N sulphuric acid and the solution was heated on the steam bath for 15 min to give 2-allyl-1-naphthol, identified as the *p*-nitrobenzoate, m.p. 98–99°, and on admixture with an authentic sample.

1-Naphthoxypropanone and 2-naphthoxypropanone were prepared according to Calaway and Henze.[36] Rearrangement of these ethers was attempted without solvent, under nitrogen, in sealed tubes at 280°. After 3 hr, the 1-naphthoxy ether had almost completely decomposed and the product was mainly 1-naphthol (identified chromatographically) with some tar. The 2-naphthoxy ether gave only a small amount of 2-naphthol under these conditions.

Kinetic studies

1% solutions of the allyl ethers in iso-octane were sealed in a series of glass tubes under nitrogen and heated at temperatures necessary to give rearrangements of between about 10 and 60% (these being decided from previous pilot runs). N-allyl-1-naphthylamine was rearranged without solvent because of the high temperatures required. Tubes were removed at intervals and the contents analysed directly by ascending reversed phase paper chromatography. The kinetic data are given in Tables 2, 3, 4, 5, 6, 7 and 8.

Analytical methods

The paper chromatographic system is based on that previously described for tocopherol analysis.[37,38] Strips of Whatman No. 4 filter paper (3 × 20 cm) were impregnated with zinc carbonate and then with liquid paraffin. The mobile phase was 40% aqueous ethanol for the naphthols, naphthylamine and 8-hydroxyquinoline derivatives, and 50% aqueous ethanol for the phenanthrols. Visualization of the chromatograms was accomplished by incorporating a trace of sodium fluorescein in the zincammine solution used for paper impregnation.[38] When viewed under ultra-violet light (Hanovia "Chromatolite"), the phenols appear as dark bands against a fluorescent background. The naphthylamines fluoresce strongly in ultra-violet light and incorporation of sodium fluorescein was omitted from the preparation of papers on which these were run. For analysis, 0·04 ml of each

[36] P. K. Calaway and H. R. Henze, *J. Amer. Chem. Soc.* **61**, 1355 (1939).
[37] J. Green, S. Marcinkiewicz and P. R. Watt, *J. Sci. Fd. Agric.* **6**, 274 (1955).
[38] J. Green, *J. Sci. Fd. Agric.* **9**, 801 (1958).

solution was chromatographed (the naphthylamine ether was dissolved to give a 1% solution in iso-octane *after* rearrangement). Chromatograms were run for 1 hr, which time was sufficient for the clear separation of the allyl-substituted phenols from the allyl ethers (the latter staying on the starting line). The R_f value of each pure allyl-substituted phenol was determined by chromatography on separate strips. Quantitative determination of each rearrangement product followed the procedures previously described.[27,28] Each band was cut out, eluted with 3 ml ethanol and the phenol determined

TABLE 9. SPECTROSCOPIC DATA ON ALLYL-SUBSTITUTED REARRANGEMENT PRODUCTS

Compound	λ_{max} (mμ)	$E^{1\%}_{1cm}$
1-allyl-2-hydroxynaphthalene	335	132
2-allyl-1-hydroxynaphthalene	325	158
1-allyl-2-hydroxyphenanthrene	343	92
4-allyl-3-hydroxyphenanthrene	346	97
10-allyl-9-hydroxyphenanthrene	333	128
7-allyl-8-hydroxyquinoline	315	122
2-allyl-1-naphthylamine	330	294

spectrophotometrically. The extinction coefficient at a suitable peak was determined on each pure compound and the data is given in Table 9. In separate experiments, each compound was studied for possible losses on chromatography: these were found to be negligible (less than 3%).

The method, however, could not be used for a study of more volatile phenols: for example, the rearrangement of allyloxybenzene cannot be studied by chromatographic methods. Since 10-allyl-9-hydroxyphenanthrene was unstable in the presence of air, particular care had to be taken during its investigation. Chromatograms of the rearrangement of 9-allyloxyphenanthrene were not dried for visualization purposes but were compared directly with other simultaneously run duplicate chromatograms visualized after drying. By this means, the position of the phenanthrol was obtained rapidly and the wet papers were cut up for quantitative determination.

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THE INTENSITIES OF THE CARBONYL BANDS IN THE INFRA-RED SPECTRA OF 2- AND 4-QUINOLONES

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Abstract—The intensities of the carbonyl bands in the infrared spectra of sixty-five 2- or 4-quinolones have been measured. The results indicate that the high intensities of 2-quinolones distinguish them from 4-quinolones. Some applications in alkaloid chemistry are discussed, including proof that the ring system of maculosidine (XXVII) is linear.

IT is often important in the chemistry of quinoline alkaloids to distinguish between a 2- and 4-quinolone. The different criteria which have been adopted for this purpose have recently been summarised by Rapoport and Holden.[1] One distinction was based on the infra-red spectra of model compounds, amongst which 2-quinolones were found to absorb at 1660–1650 cm^{-1}, and 4-quinolones at 1630–1620 cm^{-1}.[2,3] However, increasing numbers of 2- and 4-quinolones have since been found which absorb in the same frequency region, namely 1647–1631 cm^{-1}.[4,5] It has been noticed, on the other hand, that the 2-quinolone absorption band has a characteristic shape and high intensity,[5] and it is now shown that 2- and 4-quinolones may be differentiated by measuring the carbonyl intensities.

The determination of infra-red spectra in the solid state suffers from the disadvantage that frequency and relative intensity changes are often observed, depending on the state of division of the sample.[6] Owing to the low solubility of many quinolones in common infra-red solvents, very few quinolones have had their spectra measured in solution. The author has tested methylene bromide and bromoform as solvents, but many quinolones, notably 4-quinolones and 4-hydroxy-2-quinolones are sparingly soluble even in these. It was found, however, that almost all the quinolones which were tried, were soluble in dimethylsulphoxide. This has only low absorption in the carbonyl region and would be a suitable solvent but for the fact that it dissolves, to a significant extent, the potassium bromide of which cells are generally composed. However, potassium bromide was found to be virtually insoluble in mixtures of 1 part dimethylsulphoxide with 3 or 4 parts of chloroform. These mixtures readily dissolved the quinolones and, where spectra could be obtained in chloroform or methylene bromide as well as in the sulphoxide–chloroform mixture, results proved to be similar.

Integrated intensities were calculated by the method of Cabana and Sandorfy.[7] In the few cases where shoulders occurred on the high frequency side of bands, these were included in the intensity calculations using the Cabana–Sandorfy treatment for

[1] H. Rapoport and K. G. Holden, *J. Amer. Chem. Soc.* **82**, 4395 (1960).
[2] B. Witkop, J. P. Patrick and M. Rosenblum, *J. Amer. Chem. Soc.* **73**, 2641 (1951).
[3] M. F. Grundon, N. J. McCorkindale and M. N. Rodger, *J. Chem. Soc.* 4284 (1955).
[4] J. R. Price and J. B. Willis, *Aust. J. Chem.* **12**, 589 (1959).
[5] M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.* 2177 (1957).
[6] R. N. Jones and C. Sandorfy, *Technique of Organic Chemistry* Vol IX, pp. 294–297. Interscience, New York (1956).
[7] A. Cabana and C. Sandorfy, *Spectrochim. Acta* **16**, 335 (1960).

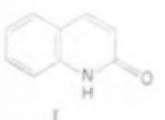
TABLE 1. INTEGRATED BAND INTENSITIES (IN ABSOLUTE UNITS) OF 2-QUINOLONES AND N-METHYL-2-QUINOLONES

No.	Structure	ν_{max} (cm^{-1})	ε^a_{max}	$A_s\dagger \times 10_7$	$A_{1/4}\dagger \times 10^7$	$A_{1/2}\dagger \times 10^7$	$A_m\dagger \times 10_7$
1	I	1658[a]*	1451	48·8	53·1	62·0	50·5
		1659[c]*	1528	51·6	54·1	63·3	53·2
2	I, 4-NHPh[9,10]	1645[a]	1854	42·6	43·5	49·4	46·1
3	II[11]	1641[a]	1274	39·4	39·8	47·7	42·2
4	II, 8-MeO[11]	1640[b]	1734	65·8	68·7	68·7	65·5
5	II, 7-MeO[12]	1642[a]	1201	51·8	53·8	60·2	55·5
6	II, 5:8-diMeO[11]	1649[c]	2047	56·8	55·6	54·9	56·8
7	II, 8-Ph[11]	1634[b]	1676	76·7	77·8	84·0	79·3
8	II, 5:6-benzo[11]	1640[a]	1550	67·2	67·9	80·9	75·6
9	II, 8-MeO_2C[11]	1637[a]	1603	61·6	63·4	71·6	66·1
10	III, 4-OH[9,9]	1640[d]	1658	45·7	44·1	42·9	43·4
11	IV[9,9]	1656[d]	2061	47·7	44·6	48·2	47·8
12	V[9,12]	1644[d]	1717	51·6	49·5	57·7	54·1
13	VI[14]	1660[a]	1358	46·3	47·4	45·9	46·1
14	VI, 8-MeO[15]	1657[b]	1674	55·6	60·3	64·8	58·3
		1657[c]	1630	51·8	55·3	60·2	54·1
15	VI, 7-MeO[14]	1657[c]	1438	52·0	55·5	59·2	55·8
16	VI, 5:8-diMeO[15]	1655[c]	1714	61·1	62·6	72·0	66·2
17	VI, 8-Ph[15]	1657[c]	1406	46·6	47·0	55·3	50·0
18	VI, 8-MeO_2C[14]	1658[c]	1636	60·3	58·1	69·2	64·5
19	VI, 5:6-benzo[15]	1658[a]	1614	59·2	60·5	72·1	63·1
20	VII	1654[c]	1436	57·6	58·5	69·4	58·2
21	VII, 5:8-diMeO	1651[c]	1526	59·6	58·9	69·6	63·3
22	VII, 8-MeO_2C	1653[c]	1428	62·4	57·4	72·0	66·5

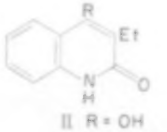
* Peaks marked with an asterisk had a shoulder on the high frequency side of the main band. This was included in the calculations.

† A_s is the value of the integrated intensity computed by the method of segments. $A_{1/4}$ and $A_{1/2}$ are those based on $\Delta\nu^0_{1/4}$ and $\Delta\nu^0_{1/2}$. A_m is the mean of $A_{3/4}$, $A_{1/2}$, $A_{1/4}$ and $A_{1/8}$.

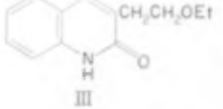
[a] Chloroform-dimethylsulphoxide (3:1)
[b] Chloroform-dimethylsulphoxide (4:1)
[c] Chloroform
[d] Methylene bromide



I



II R = OH
VI R = $OCOCH_3$
VII R = Cl
VIII R = OMe

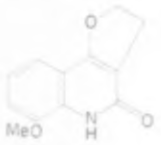


III

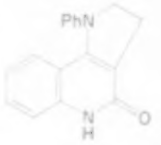
[9] Sample kindly provided by Dr. M. F. Grundon, Queen's University, Belfast.
[10] F. H. S. Curd, C. G. Raison and F. L. Rose, *J. Chem. Soc.* 899 (1947).
[11] Preparation as for compound no. 5 (*cf.* ref. 12).
[12] R. G. Cooke and H. F. Haynes, *Aust. J. Chem.* **7**, 273 (1954).
[13] M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.* 3448 (1957).
[14] T. Ohta, *J. Pharm. Soc. Japan* **73**, 63 (1953).
[15] Preparation as for compound no. 13 (*cf.* ref. 14).

TABLE 1 (*contd.*)

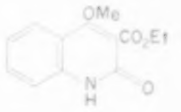
No.	Structure	ν_{max} (cm^{-1})	ε^{a}_{max}	A_s $\times 10^7$	$A_{1/4}$ $\times 10^7$	$A_{1/2}$ $\times 10^7$	A_m $\times 10^7$
23	VII, 8-MeO	1653[c]	1324	50·9	52·4	59·2	54·6
24	III, 4-Cl[8,9]	1651[d]	1510	52·2	52·3	58·5	54·8
25	I, 3-HO_2C[16]	1638[a,e]	1008	33·7	42·1	30·5	33·0
26	I, 4-HO_2C[17]	1666[a]	1431	49·3	50·8	56·3	51·4
27	VIII[14]	1650[c]	1443	53·0	58·7	59·8	55·8
28	VIII, 8-MeO[18]	1648[c]	1761	59·2	58·8	66·6	62·6
29	VIII, 7-MeO[18]	1647[c]	1402	54·9	57·0	62·7	59·3
		1649[b]	1426	47·7	47·6	58·7	51·4
30	VIII, 6-MeO[18]	1650[c]	1339	42·0	44·0	45·2	43·9
31	VIII, 5:8-diMeO[18]	1646[c]	1741	62·6	63·2	74·1	68·2
		1648[b]	1552	57·2	56·7	69·4	63·9
32	VIII, 6:8-diMeO[18,19]	1648[c]	1273	34·3	35·8	37·3	35·5
33	VIII, 8-Ph[18]	1648[c]	1510	56·4	58·3	67·5	61·2
34	IX[3]	1651[a]	1391	56·3	55·9	61·0	58·5
		1649[d]	1498	53·7	54·3	58·5	57·2
35	X[20]	1652[a,e]	1297	34·7	38·0	37·4	36·8
36	XI	1638[a,e]	1366	41·3	45·3	45·9	40·7
37	XII[14]	1630[b]	1042	45·2	42·9	54·0	49·4
38	XII, 8-MeO_2C[21]	1632[a]	1137	38·8	41·5	46·8	41·8
39	XII, 7-MeO[12]	1626[a]	1076	38·9	41·4	48·2	41·7
40	XIII[21]	1639[a]	1353	41·7	46·6	52·3	43·2
41	XIV[21]	1636[c]	1269	35·5	35·7	38·6	37·5
		1635[a]	1205	36·3	37·7	37·4	36·8
42	XIV, 7-MeO[21]	1632[c]	1292	41·3	41·8	46·2	42·6
43	XIV, 8-MeO_2C[21]	1640[b]	1352	53·2	52·2	60·4	55·2
44	XV[22]	1659[d]	1787	60·3	59·7	67·1	62·9



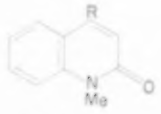
IV



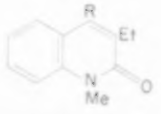
V



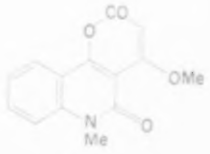
IX



X R = H
XI R = OH
XIII R = OMe



XII R = OH
XIV R = OMe



XV

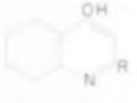
[16] P. Friedlander and C. F. Goering, *Ber. Dtsch. Chem. Ges.* **17**, 459 (1884).
[17] Sample kindly supplied by Dr. J. D. Loudon, Glasgow University.
[18] Preparation as for compound no. 27 (*cf.* ref. 14).
[19] R. H. Prager, E. Ritchie and W. C. Taylor, *Aust. J. Chem.* **13**, 385 (1960).
[20] Sample kindly supplied by Dr. A. Kent, Glasgow University.
[21] Preparative method as in ref. 12.
[22] M. F. Grundon and N. J. McCorkindale, unpublished work. *Cf.* R. E. Bowman, A. Campbell and E. M. Turner, *J. Chem. Soc.* 444 (1959).

TABLE 2. INTEGRATED BAND INTENSITIES (IN ABSOLUTE UNITS) OF 4-QUINOLONES AND N-METHYL-4-QUINOLONES

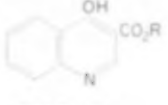
No.	Structure	ν_{max} (cm^{-1})	ε^{a}_{max}	A_s $\times 10^7$	$A_{1/4}$ $\times 10^7$	$A_{1/2}$ $\times 10^7$	A_m $\times 10^7$
45	XVI[23]	1635[b]	689	21·5	20·1	21·4	20·9
		1636[a]	580	16·3	17·0	17·5	16·4
46	XVI, 8-MeO[24]	1632[a]	501	10·3	9·9	10·5	10·2
47	XVII[17,25]	1638[a]	524	14·9	17·1	16·8	15·8
48	XVII, 5:8-diMeO[25]	1639[a]	883	22·1	20·3	20·3	21·1
49	XVII, 6:8-diCl[17,25]	1639[a]	671	16·2	15·7	18·2	17·8
50	XVIII,[26]	1633[a]	676	8·9	9·9	10·9	9·7
51	XIX[23]	1624[a]	794	22·6	22·4	28·2	24·5
52	XIX, 8-Ph[27]	1629[c]	615	25·1	25·0	30·3	27·3
		1626[a]	682	25·8	25·6	27·9	26·6
53	XIX, 8-MeO_2C[28]	1645[a]	413			12·4*	
54	XIX, 8-MeO[24]	1622[a]	412	13·1	12·9	15·7	14·4
55	XX, 5:8-diMeO[27]	1629[a]	819	24·6	25·7	29·1	25·8
56	XXI[17]	1632[a]	421	12·9	12·3	12·7	12·7
57	XXI, 7-Cl[17]	1632[a]	620	21·8	21·3	20·3	21·1
58	XXII[17]	1630[a]	460			13·9*	
59	XXII, 6-Cl[17]	1633[a]	572			20·7*	
60	XVI, 8-Ph[27,29]	1629[c]	1390	22·2	21·3	22·1	21·7
61	XVI, 7:8-benzo[27,30]	1632[a]	1169	18·8	20·1	20·1	19·5
62	XXIII, 8-Ph[31]	1628[a]	991	22·0	23·8	26·2	23·7
63	XXIII, 2-Me[31]	1624[a]	952	20·5	22·3	24·1	21·8
64	XXIII, 2-Ph[32]	1622[a]	722	16·6	16·9	22·3	18·6
65	XXIII[31,33]	1629[a]	760	20·5	22·2	25·6	22·2

* In this case it was not found possible to measure the quarter and eighth band widths owing to the presence of an adjoining peak on both sides of the carbonyl band.

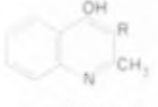
[a] Chloroform-dimethylsulphoxide (3:1) [b] Chloroform-dimethylsulphoxide (4:1) [c] Chloroform



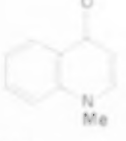
XVI R = H
XVII R = Me
XVIII R = Ph



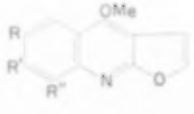
XIX R = Et
XX R = H



XXI R = CO_2Et
XXII R = $COCH_3$



XXIII



XXIV R = R′ = R″ = H
XXV R = R′ = H, R″ = OMe
XXVI R = R″ = H, R′ = OMe
XXVII R = R″ = OMe, R′ = H

[23] C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.* **68**, 1204 (1946)
[24] W. M. Lauer R. T. Arnold, B. Tiffany and J. Tinker, *J. Amer. Chem. Soc.* **68**, 1268 (1946).
[25] M. Conrad and L. Limpach, *Ber. Dtsch. Chem. Ges.* **21**, 1965 (1888).
[26] R. C. Fuson and D. M. Burness, *J. Amer. Chem. Soc.* **68**, 1270 (1946)
[27] Preparation by the Price–Roberts method (*cf.* ref. 23).
[28] M. F. Grundon and V. Boekelheide, *J. Amer. Chem. Soc.* **74**, 2637 (1952).
[29] C. E. Kaslow and M. Hayek, *J. Amer. Chem. Soc.* **73**, 4986 (1951).
[30] R. E. Foster, R. D. Lipscomb, T. J. Thompson and C. S. Hamilton, *J. Amer. Chem. Soc.* **68**, 1327 (1946
[31] Methylation as in the preparation of compound no. 64 (*cf.* ref. 32).
[32] R. Johnstone, J. R. Price and A. R. Todd, *Aust. J. Chem.* **11**, 562 (1958).
[33] E. Spath and A. Kolbe, *Monatsh.* **53**, 421 (1922).

unsymmetrical bands. Shoulders on the low frequency side were not included, since these might be attributable to ring vibrations. Intensities are given in absolute units, cm, c/s, molecule, ln.

The results given in Tables 1–2 support the generalization that the amide carbonyl absorption of 2-quinolones is considerably more intense than that of 4-quinolones. The carbonyl intensities found for the 4-quinolones (8·9–25·8 units) are comparable to those found for a group of anilides (Table 3), and to those recorded[8] for some acetamides, benzamides and acetanilides (11·6–22·5 units). The carbonyl intensities of the 2-quinolones lie in a higher range (33·7–76·7 units). Accordingly, despite the fact that a number of the 2- and 4-quinolones examined absorb in the same frequency range (1649–1626 cm^{-1}), the high peak intensities of the 2-quinolones allow them to be distinguished from the 4-quinolones.

The apparent molecular extinction coefficients (ε^a_{max}) corresponding to the carbonyl absorption are again large in the case of 2-quinolones (1000–2000). Although the majority of the 4-quinolones had ε^a_{max} values considerably less than 900, four had higher values (compounds nos. 60–63), and, on the basis of ε^a_{max} value alone, would be indistinguishable from 2-quinolones. The carbonyl bands of these were, however, narrow and the integrated areas were therefore similar to those of other 4-quinolones.

Comparing the results obtained by the different methods of intensity estimation (Tables 1–2), it may be seen that intensity values given by $A_{1/4}$ (i.e. based on $\Delta\nu^a_{1/4}$, the apparent quarter band width) and by A_m (the mean of $A_{3/4}$, $A_{1/2}$, $A_{1/4}$ and $A_{1/8}$) allow the same empirical classification of the quinolones as the more accurate values given by the method of segments (A_s). $A_{1/2}$ is not quite so satisfactory in this respect. The results agree with the suggestion of Cabana and Sandorfy[7] that, for symmetrical bands, $A_{1/4}$ is a more useful approximation of the intensity than $A_{1/2}$.

The structures of some of the quinolones examined are relevant to the structures of different alkaloids. The carbonyl intensities of ethyl dictamnate (IX) (53·7 units), derived from the alkaloid dictamnine (XXIV), and of 2-phenyl-4-quinolone (8·9 units) and 1-methyl-2-phenyl-4-quinolone* (16·6 units), derived from the alkaloid 4-methoxy-2-phenylquinoline,[34] are in accord with their respective structures.

Hydrogenolysis of many furoquinoline alkaloids gives rise to a 3-ethyl-4-methoxy-2-quinolone, which may be synthesised.[35] It is assumed in the synthesis that diazomethane effects selective methylation of the 4-hydroxy group in the corresponding 4-hydroxy-2-quinolone. If the 2-quinolone structure of these hydrogenolysis products is established, it follows that the furan oxygen in the respective alkaloids is attached to the 2- rather than the 4- position. Seven 3-ethyl-4-methoxy-2-quinolones are included in Table 1, three of which (compounds nos. 27–29) correspond to the alkaloids of established structure dictamnine (XXIV),[5] fagarine (XXV)[5] and evolitrine (XXVI)[36] respectively. The high carbonyl intensities of these three quinolones (47·7–59·2 units) reaffirms their 2-quinolone structure.

The structure of the alkaloid maculosidine, however, has not been established rigorously, and the linear arrangement of its ring system rests on the properties of the hydrogenolysis product, assigned the structure XXVII on spectral grounds (λ_{max} 280 mμ, ν_{max} (in Nujol) 1646 cm^{-1}). Compound no. 32, synthesized during the

* This compound has also been isolated recently from natural sources.[1]

[8] H. W. Thompson and D. A. Jameson, *Spectrochim. Acta* **13**, 236 (1958).

TABLE 3. INTEGRATED BAND INTENSITIES (IN ABSOLUTE UNITS) OF ANILIDES

No.	Structure	ν_{max} (cm^{-1})	ε^a_{max}	A_0 $\times 10^7$	$A_{1/4}$ $\times 10^7$	$A_{1/2}$ $\times 10^7$	A_∞ $\times 10^7$
66	Acetanilide	1682[b]	447	14·9*	16·3	19·5	17·7
67	*p*-Cl-acetanilide[17]	1686[a]	405	14·9*	15·2	16·2	15·5
68	*p*-MeO-acetanilide	1684[b]	475	18·9*	19·3	20·8	19·9
		1676[a]	509	19·0	19·5	21·6	20·4
69	*o*-Cl-acetanilide[17]	1693[a]	319	16·4	19·5	20·0	19·8
70	2:4-diMeO-acetanilide[17]	1680[a]	351	13·8	14·1	17·3	15·7
71	α-Et-malon-di-*o*-anisidide†	1681[a]	324	15·3	16·9	15·2	15·5

* Thompson and Jameson[8] report the integrated intensities of compounds no. 66–68 as 15·1, 14·7 and 16·8 units respectively (chloroform solutions).
† Intensity per carbonyl group.
[a] Chloroform-dimethylsulphoxide (3:1).
[b] Chloroform.

present work, was identical with an authentic sample of the hydrogenolysis product. It was found that in KBr, the carbonyl frequency was unexpectedly low, 1626 cm^{-1}. However, the method of synthesis and the high carbonyl intensity (34·3 units) of this compound confirm it as a 2-quinolone, and hence the linear structure of the alkaloid.

EXPERIMENTAL

The infra-red spectra were determined on a Unicam SP100 instrument (Mark II), using a diffraction grating and with spectral slit widths of 4·0–4·7 cm^{-1}. The measurements were carried out on 6–12 mg samples dissolved in 5 cm^3 of solvent, using 0·5 mm cells.

The compounds examined were purified commercial samples or were prepared by standard methods. References to known compounds and preparative methods are included in Tables 1–3, and the properties of new compounds are noted briefly below.

M.p.s were measured on a Kofler block and are uncorrected.

3-*Ethyl*-4-*hydroxy*-8-*methoxy*-2-*quinolone*. (II, 8-MeO). M.p.226–227° (alcohol). (Found: C, 66·0; H, 5·7; N, 6·2. $C_{12}H_{13}O_3N$ requires: C, 65·7; H, 6·0; N, 6·4%).

3-*Ethyl*-4-*hydroxy*-5:8-*dimethoxy*-2-*quinolone* (II, 5:8-diMeO). M.p.217–218° (alcohol). (Found: C, 62·4; H, 5·7; N, 5·5. $C_{13}H_{15}O_4N$ requires: C, 62·6; H, 6·1; N, 5·6%).

3-*Ethyl*-4-*hydroxy*-8-*phenyl*-2-*quinolone* (II, 8-Ph). M.p.233–235° (alcohol). (Found: C, 76·7; H, 5·4; N, 5·4. $C_{17}H_{15}O_2N$ requires: C, 77·0; H, 5·7; N, 5·3%).

5:6-*Benzo*-3-*ethyl*-4-*hydroxy*-2-*quinolone* (II, 5:6-benzo). M.p.270–275° (acetic acid). (Found: C, 75·6; H, 5·4; N, 6·0. $C_{15}H_{13}O_2N$ requires: C, 75·3; H, 5·5; N, 5·9%).

3-*Ethyl*-4-*hydroxy*-8-*methoxycarbonyl*-2-*quinolone* (II, 8-MeO_2C). M.p.245° (alcohol). (Found: C, 63·2; H, 4·8; N, 5·5. $C_{13}H_{13}O_4N$ requires: C, 63·2; H, 5·3; N, 5·7%).

4-*Acetoxy*-3-*ethyl*-8-*methoxy*-2-*quinolone* (VI, 8-MeO). M.p.180–182° (alcohol). (Found: C, 64·4; H, 5·6. $C_{14}H_{15}O_4N$ requires: C, 64·4; H, 5·8%).

4-*Acetoxy*-3-*ethyl*-7-*methoxy*-2-*quinolone* (VI, 7-MeO). M.p.223° (aqueous alcohol). (Found: C, 64·1; H, 5·9. $C_{14}H_{15}O_4N$ requires: C, 64·4; H, 5·8%).

4-*Acetoxy*-3-*ethyl*-5:8-*dimethoxy*-2-*quinolone* (VI, 5:8-diMeO). M.p.184–188° (aqueous alcohol). (Found: C, 62·0; H, 6·0. $C_{16}H_{17}O_5N$ requires: C, 61·9; H, 5·9%).

4-*Acetoxy*-3-*ethyl*-8-*phenyl*-2-*quinolone* (VI, 8-Ph). M.p.215–217° (alcohol). (Found: C, 74·3; H, 5·5. $C_{19}H_{17}O_3N$ requires: C, 74·3; H, 5·6%).

4-*Acetoxy*-3-*ethyl*-8-*methoxycarbonyl*-2-*quinolone* (VI, 8-MeO_2C). M.p.171–172° (alcohol). (Found: C, 62·5; H, 5·0. $C_{15}H_{15}O_5N$ requires: C, 62·3; H, 5·2%).

4-*Acetoxy*-5:6-*benzo*-3-*ethyl*-2-*quinolone* (VI, 5:6-benzo). M.p.266–271° (alcohol). (Found: C, 72·8; H, 5·2; N, 5·1. $C_{17}H_{15}O_3N$ requires: C, 72·6; H, 5·4; N, 5·0%)

[34] S. Goodwin, A. F. Smith, and E. C. Horning, *J. Amer. Chem. Soc.* **79**, 2239 (1957).
[35] T. Ohta and Y. Mori, *Ann. Rep. Tokyo Coll. Pharm.* **5**, 48 (1955).
[36] T. Ohta and Y. Mori, *J. Pharm. Soc. Japan* **78**, 446 (1958).

4-Chloro-3-ethyl-2-quinolones (compounds nos. 20–23) were prepared conveniently in 50–60% overall yield from the appropriate 3-ethyl-4-hydroxy-2-quinolone by successive treatments with phosphorus oxychloride and acetic acid.[37] When, however, this process was applied to 3-ethyl-4-hydroxy-2-quinolone (II, 8-Ph), a 55% yield of 4-acetoxy-3-ethyl-8-phenyl-2-quinolone was obtained, identical (m.p., mixed m.p. and infra-red spectrum) with a sample prepared as above.

4-Chloro-3-ethyl-2-quinolone (VII). M.p.222–225° (aqueous alcohol). (Found: C, 63·6; H, 4·9. $C_{11}H_{10}ONCl$ requires: C, 63·6; H, 4·9%).

4-Chloro-3-ethyl-5:8-dimethoxy-2-quinolone (VII, 5:8-diMeO). M.p.201–204° (alcohol). (Found: 58·1; H, 5·0. $C_{13}H_{14}O_3NCl$ requires: C, 58·3; H, 5·3%).

4-Chloro-3-ethyl-8-methoxycarbonyl-2-quinolone (VII, 8-MeO_2C). M.p. 142–142·5° (aqueous alcohol). (Found: C, 58·9; H, 4·2. $C_{13}H_{12}O_3NCl$ requires: C, 58·8; H, 4·6%).

4-Chloro-3-ethyl-8-methoxy-2-quinolone (VII, 8-MeO). M.p. 206–208° (alcohol). (Found: C, 60·6; H. 5·2. $C_{12}H_{12}O_2NCl$ requires: C, 60·6; H, 5·1%).

3-Ethyl-4:8-dimethoxy-2-quinolone (VIII, 8-MeO). M.p.116–118° (light petroleum, b.p. 60–80°). (Found: C, 67·1; H, 6·4. $C_{13}H_{15}O_3N$ requires: C, 66·9; H, 6·5%).

3-Ethyl-4:7-dimethoxy-2-quinolone (VIII, 7-MeO). M.p. 152·5–154° (benzene–light petroleum). (Found: C, 67·4; H, 6·3. $C_{12}H_{13}O_3N$ requires: C, 66·9; H, 6·5%).

3-Ethyl-4:6-dimethoxy-2-quinolone (VIII, 6-MeO). M.p. 167–169° (benzene–light petroleum). (Found: C, 66·9; H, 6·6; N, 6·3. $C_{12}H_{15}O_3N$ requires: C, 66·9; H, 6·5; N, 6·0%).

3-Ethyl-4:5:8-trimethoxy-2-quinolone (VIII, 5:8-diMeO). M.p. 149–150° (benzene–light petroleum). (Found: C, 64·0; H, 6·4. $C_{14}H_{17}O_4N$ requires: C, 63·9; H, 6·5%).

3-Ethyl-4:6:8-trimethoxy-2-quinolone (VIII, 6:8-diMeO). M.p. 130–131° (light petroleum, b.p. 60–80°). (Found: C, 64·0; H, 6·6; N, 5·5. Calc. for $C_{14}H_{17}O_4N$: C, 63·9; H, 6·5; N, 5·3%). There was no depression in m.p., on admixture with an authentic sample* of the hydrogenolysis product of maculosidine, m.p. 130–131°†. The ultra-violet and infra-red spectra of the product were identical with those of the authentic sample.

3-Ethyl-4-methoxy-8-phenyl-2-quinolone (VIII, 8-Ph). M.p. 135–136° (light petroleum, b.p. 60–80°). (Found: C, 77·6; H, 5·8. $C_{18}H_{17}O_2N$ requires: C, 77·4; H, 6·1%).

3-Ethyl-4-hydroxy-8-methoxycarbonyl-1-methyl-2-quinolone (XII, 8-MeO_2C). M.p. 242–243° (aqueous alcohol). (Found: C, 64·4; H, 5·4; OMe, 11·4. $C_{14}H_{15}O_4N$ requires: C, 64·4; H, 5·8; one OMe, 11·9%).

3-Ethyl-4-methoxy-1-methyl-2-quinolone (XIV). M.p. 82–83·5° (light petroleum, b.p. 40–60°). (Found: C, 71·9; H, 6·9. $C_{13}H_{15}O_2N$ requires: C, 71·9; H, 7·0%).

3-Ethyl-4:7-dimethoxy-1-methyl-2-quinolone (XIV, 7-MeO). B.p. 160–180° (bath temp.)/0·1 mm, m.p. 72–74° (light petroleum, b.p. 40–60°). (Found: C, 68·1; H, 6·9. $C_{14}H_{17}O_3N$ requires: C, 68·0; H, 6·9%).

3-Ethyl-4-methoxy-8-methoxycarbonyl-1-methyl-2-quinolone (XIV, 8-MeO_2C). M.p. 119–120° (light petroleum b.p. 40–60°). (Found: C, 65·4; H, 6·1. $C_{15}H_{17}O_4N$ requires: C, 65·4; H, 6·2%).

5:8-Dimethoxy-2-methyl-4-quinolone (XVII, 5:8-diMeO). M.p. 216–217° (dimethylformamide.) (Found: C, 65·9; H, 5·8; N, 6·6. $C_{12}H_{13}O_3N$ requires: C, 65·7; H, 6·0; N, 6·4%).

3-Ethoxycarbonyl-8-phenyl-4-quinolone (XIX, 8-Ph). M.p. 245–248° (pyridine–alcohol). (Found: C, 73·7; H, 5·0; N, 5·1. $C_{18}H_{15}O_3N$ requires: C, 73·7; H, 5·2; N, 4·8%).

3-Carboxy-5:8-dimethoxy-4-quinolone (XX, 5:8-diMeO). M.p. 270–271° (acetone). (Found: C, 57·5; H, 4·6; N, 5·5. $C_{12}H_{11}O_5N$ requires: C, 57·8; H, 4·5; N, 5·6%).

8-Phenyl-4-quinolone (XVI, 8-Ph). M.p. 203·5–204·5°‡ (aqueous alcohol). (Found: C, 81·1; H, 4·8; N, 6·5. Calc. for $C_{15}H_{11}ON$: C, 81·4; H, 5·0 N, 6·3%).

α-Ethyl-malondi-o-anisidide. M.p. 152–154° (alcohol). (Found: C, 67·1; H, 6·6; N, 8·1. $C_{19}H_{22}O_4N_2$ requires: C, 66·7; H, 6·5; N, 8·2%).

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* The author is indebted to Dr. E. Ritchie, University of Sydney for this sample.

† Prager *et al.*[19], give m.p. 126–127°.

‡ Kaslow and Hayek[20] give m.p. 204°.

[37] T. Sato and M. Ohta, *Bull. Chem. Soc. Japan* **30**, 708 (1957).

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THE INTERACTION CURVE OF NON-BONDED CARBON AND HYDROGEN ATOMS AND ITS APPLICATION

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Abstract—A universal interaction curve of non-bonded carbon and hydrogen atoms has been proposed. This curve has been successfully applied to determine numerous properties of various saturated and unsaturated hydrocarbons such as the equilibrium of molecular conformation, the strain energy of molecules, the sublimation heat of organic crystals and so on.

1. INTRODUCTION

IN dealing with problems of physical chemistry it is advantageous to consider the molecule as a system of interacting atoms. The approximate additivity of molecular properties, the low interdependence of valence angles and bonds during the vibration of the molecule as well as many other arguments permits the separation of the inner potential molecular energy into three parts: the bond energy, the interaction energy of non-bonded atoms and the energy of deviation of angles from their ideal value. The energy of atomic interaction within the molecule must therefore involve the sum of energies from all atom pairs and that of directed valency must be taken as the sum of $\frac{1}{2}C\alpha^2$ stress in all valency angles of the molecule.

As to the molecular interaction energy (for a substance in a condensed state) it must be estimated as the overall interaction energy of all atomic pairs of different

* Translated by A. L. Pumpiansky, Moscow.

molecules. We shall henceforth assume no difference between the interaction curves of non-bonded 'neutral' atoms belonging to the same or different molecules.

For this theory to be applicable to various problems of reactivity, kinetics, adsorption, thermal chemistry, and others, it is necessary to have data for the curves of interaction energy of non-bonded atoms.

The most precise X-ray studies of the electronic density distribution in crystals show that within the precision of 0·1 to 0·2 electrons, the electronic density of chemically bonded atoms can be represented by a spherically symmetric function. This can be considered as some justification for regarding a molecule as a system of interacting atoms.

If the atoms of the molecule are electrically charged then the expression of the energy should also include the electrostatic interactions. Mostly, however, the electric interactions are of no importance. Thus, for example, in the interaction energy of molecules in a crystal the dipole interaction does not exceed a few per cent. As the electric potential varies slowly it will not play any important part in the study of conformation. There is also a large class of molecules whose atomic charges are practically equal to zero. We are essentially concerned with the interaction curve of 'neutral' non-bonded atoms.

In terms of the well known theoretical derivation of the interaction energies at great distances the interaction energy may be written as $Ar^{-6} - Br^{-n}$ or $Ar^{-6} - B\exp\left(-\frac{r}{\rho}\right)$ these expressions being often used for various calculations.

The interaction energy of non-bonded atoms affects a large number of different phenomena. Its magnitude determines partly the heat of combustion, it is essentially responsible for the stereochemical configuration of the molecules, its magnitude fully accounts for the intermolecular interaction which defines the values of heats of sublimation and adsorption, equilibrium distances in crystals, etc.

In organic chemistry different combinations of few atoms give rise to very many compounds. The question is whether there are universal constants A, B, ρ, that can be used to account for the interaction of 'neutral' atoms independent of the molecules to which they belong.

We found that with some reduced coordinates one can propose a universal curve involving the interaction C . . . C, H . . . H, and C . . . H that holds true both for saturated and unsaturated hydrocarbons.

2. THE UNIVERSAL INTERACTION CURVE OF CARBON AND HYDROGEN ATOMS

The experimentally best known parameters of the interaction curves are the intermolecular distances in the crystal. These undoubtedly hold (at least with an accuracy of 5 per cent) for all hydrocarbons and in general for all organic substances independent of their chemical nature. Taking into consideration that on entering the crystal the molecules are being slightly 'pressed', we shall assume the equilibrium distances of 'isolated' atoms to be C . . . C 3·8 Å, C . . . H 3·15 Å and H . . . H 2·6 Å. These figures indicate the equilibrium intermolecular distances in crystal C . . . C 3·6 Å and H . . . H 2·35 Å, that is, to mean experimental values.[1]

[1] A. I. Kitaygorodsky, *Organic Crystal Chemistry*. Moscow (1955).

Let us denote by $z = \frac{r}{r_0}$ the relation of the distance between the atoms to their equilibrium distance and rewrite the expression of 6-exp potential $-\frac{A}{r^6} - B\exp\left(-\frac{r}{\rho}\right)$ into

$$V = V_{2/3}\frac{\frac{1}{z^6} - \frac{6}{\alpha}e^{\alpha}e^{-\alpha z}}{11{\cdot}4 - \frac{6}{\alpha}e^{\alpha/3}}$$

where $V_{2/3}$ is the energy value at $r = \frac{2}{3}r_0$ ($\frac{2}{3}r_0$ is a typical contraction met with in organic molecules. Thus, in aliphatic chains carbon atoms bonded to the same atom are at a distance about $\frac{2}{3}r_0$).

Parameter $\alpha = \frac{r_0}{\rho}$, of $V_{2/3} = -\frac{A}{r^6}\left(11{\cdot}4 - \frac{6}{\alpha}e^{-\alpha/3}\right)$, parameter B is excluded, as usually, in terms of the equilibrium condition $B = \frac{6A}{\alpha r_0^6}e^{\alpha}$.

The above transformation substantially facilitates the search for unknown parameters and makes the problem much clearer. It is seen that $V/V_{2/3}$ is the function of only one parameter. The second parameter can be easily picked out as a scale value. It is self evident that $V_{2/3}$ is the value of the order of a few kcal/mole. It is rather

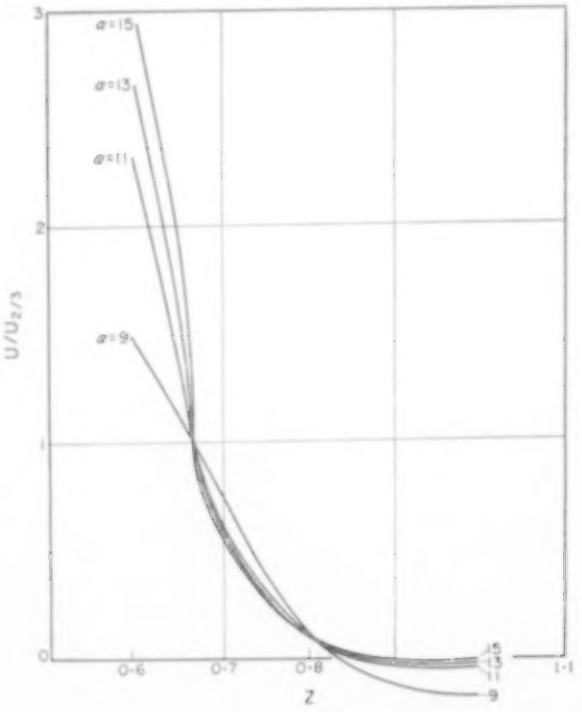

FIG. 1.

important that a reasonable range of values for α is also self evident. Indeed, calculating $V/V_{2/3}$ for $z = 1$ it is at once obvious that the interaction energy values at equilibrium (mainly determining the sublimation heat) will be reasonable only for α, that are within the 11 to 18 range. Thus the advantage of the new form of 6-exp. potential lies in the small scattering of possible values for two parameters (the third one r_0 has already been introduced into the formula).

As is seen from Fig. 1, the curve $V/V_{2/3}$ is fixed in point $z = \frac{2}{3}$, and its minimum abscissa is constant (at $z = 1$). As the value of $V/V_{2/3}$ in the minimum is very small actually the curve is fixed in two points so that the variation of α is of no special importance, the curve being hardly sensible to the parameter α. This is quite distinctly seen from the pattern.

The parameters α and $V_{2/3}$ for hydrocarbons were chosen so as to meet in the best way the existing manifold experiment.

It is of interest that the values of α and $V_{2/3}$ for all interactions seem to be very close to each other. At this initial stage of the investigation we believe it possible to make use of the universal expression (in reduced coordinates) as follows:

$$V = 3{\cdot}5\left(-\frac{0{\cdot}04}{z^6} - 8{\cdot}6 \,.\, 10^3 \,.\, e^{-13z}\right) \tag{1}$$

The choice of $\alpha = 13$ determines the values of two coefficients given in brackets. The value for $V_{2/3} = 3{\cdot}5$ kcal/mole is chosen independently.

The constants A, B and ρ for C . . . C, C . . . H, and H . . . H interactions are

	A $\frac{\text{kcal}}{\text{mole}}$ Å^6	B $\frac{\text{kcal}}{\text{mole}}$	ρÅ
C . . . C	420	$3 \,.\, 10^4$	0·29
C . . . H	140	$3 \,.\, 10^4$	0·24
H . . . H	43	$3 \,.\, 10^4$	0·20

Thus in respect to our previous work[2] we have advanced a step forward. Previously we suggested a universal expression $V'\left(\frac{\Delta r}{r}\right)$.

The present investigation indicates the possibility of applying the universal curve not only for the derivation of the energy but for the energy itself.

The previous expression $\frac{V'}{C}$ is in good agreement with the expression used in this work.

3. MOLECULAR INTERACTIONS

Our future communications will deal with the precision of the formula, elucidation of the limits of its applicability and the search for similar expressions for other atoms. Here we are concerned with the main results of the manifold application of the proposed potential.

In Fig. 2 is plotted the energy of the crystalline methane lattice calculated in terms of the formula (1). The values shown correspond to those obtained experimentally 2·6 kcal/mole for the lattice constant (5·8 Å) and the lattice energy (the experimental

[2] A. I. Kitaygorodsky, *Tetrahedron* **9**, 183 (1960).

value, calculated from the sublimation heat is equal to 2·6 kcal/mole). The asymmetry of the curve leads also to a reasonable course of the lattice parameter with changing temperature. The energy of methane in a gas-crystalline(rotation-crystalline) state, or such a state of the substance when the molecular centres form a regular lattice and the azimuthes of the molecules are random toward the crystallographic axes, is the same up to 0·2 kcal/mole.

The calculated energy of the quasicrystalline aggregation of molecules and molecules arranged in the nearest order does not markedly differ from that of the crystal.

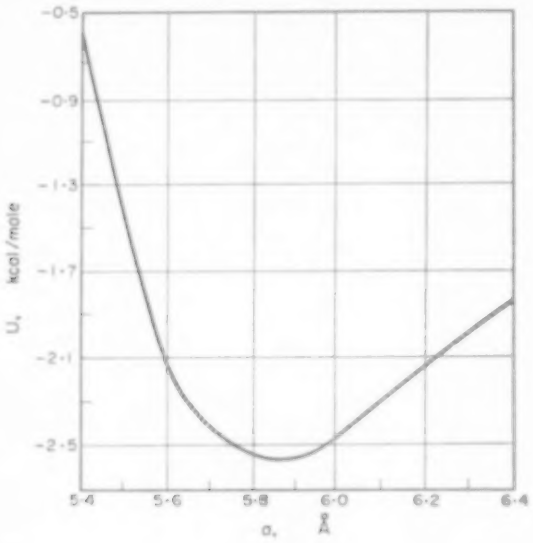

FIG. 2.

This is already seen from the fact that it changes very little with changing lattice parameter from 0°K to the melting point.

The equilibrium values of the lattice energy were calculated for other substances as well. Thus, for the gas-crystalline state of cyclopentane the calculation resulted in 7 kcal/mole rather than 8 kcal/mole obtained from the experimental value of the sublimation heat. It will be noted that for gas-crystalline cyclohexane the calculated and experimental values are markedly different, being 3 and 9·6 kcal/mole, respectively. This difference is interpreted as follows. The calculation was made allowing for a complete randomness in the molecular azimuths. But the molecule of cyclohexane is essentially different in its form from a sphere. The availability of a nearest order excludes such an arrangement of neighbours when the largest diameters of the molecules overlap. The overestimation in the calculation of "overcrowded" positions leads of course to the rise in repulsion and hence, to the rise in energy (decrease in absolute value).

The calculation of the energy in the benzene lattice is rather tedious. We have calculated[3] the contribution to the energy of the interaction of a molecule with its twelve nearest neighbours making up the first co-ordination sphere. This resulted in 6·5 kcal/mole.

[3] A. I. Kitaygorodsky and K. V. Myrskaya *Crystallographia URSS* In press.

On the basis of less cumbersome calculations carried out for gas-crystalline substances we found that the contribution to the energy of the first co-ordination sphere is 85–90 per cent. As the experimental value of the energy for the benzene lattice is 9–10 kcal/mole, the calculated and experimental values are seen to be in excellent agreement.

Our curve of the energy for atom interaction practically coincides with that of carbon atom interaction found by Crowell[4] when analysing the properties of graphite. Our curve also points to the observed decrease in the distances between the aromatic molecules when the latter increase in size. The investigation of the properties of lattices of organic crystals is the main means of obtaining the interaction curve of neutral atoms more precisely.

Besides estimating the energy and the equilibrium distance, interaction curves can also be used to obtain compressibility values. The calculation of compressibility for methane resulted in 0·16 kcal/mole Å against the experimental value 0·18.

4. INTRAMOLECULAR INTERACTIONS

To evaluate the strain energy of the molecule

$$W = \tfrac{1}{2} \Sigma C\alpha_i^2 + \Sigma V_{ik}$$

it is necessary to obtain the elasticity coefficient of the ideal angle C of the molecule.

It is possible to choose the value C for the carbon atom by making use of the data for the optical force constant. By definition $\gamma = \left[\frac{\partial^2 W}{\partial \alpha^2}\right]_{\alpha=\alpha_0}$, where α_0 is the equilibrium value, a W is the elasticity energy of the ideal angle plus the interaction energy of non-bonded atoms. To recalculate the values C corresponding to values of γ one must know the shape of the interaction curve since

$$\gamma = \frac{\partial^2 W}{\partial \alpha^2} = C + V'(r)\frac{\partial^2 r}{\partial \alpha^2} + V''(r)\left(\frac{\partial r}{\partial \alpha}\right)^2$$

The value $C = 35$ kcal/mole in combination with the expression for our potential leads to the figures $\gamma_{CCC} = 95$ kcal/mole, $\gamma_{HCH} = 79$ kcal/mole, in full accord with optical data.

Using this value of C we have calculated the values of the strain energy as well as the optimal conformations for a number of hydrocarbon molecules, the experimental and theoretical data being listed in Table 1.

The conformation data are in close agreement with those of our previous work. A new approach allowed us to estimate in addition the magnitudes of the strain energy.

As will be seen from Table 1 the main contribution to the strain energy results from the repulsion of the non-bonded atoms rather than from the deviation of the angle from its tetrahedral value. Thus, even with cyclobutane $\frac{1}{2}C\alpha^2 = 2$ kcal/mole whereas the strain energy per one CH_2 group is 21 kcal/mole. This of course should be considered as resulting from a different, and presumably more correct, definition of strain energy. In classical works strain energy is referred to as the strain energy in excess of that of alkanes. This excess strain energy is accounted for by 2/3 by the

[4] A. D. Crowell, *J. Chem. Phys.* **29**, 446 (1958).

TABLE 1

Molecule	Angles	Values of angles (deg)			Strain energy per CH_2 group kcal/mole	Excess strain energy as compared to that of alkanes	
		theoretical		Experimental			
		present work	Ref. 2			Theor.	Experim.
Ethane	HCH	109·4	—	109·3	—	—	
Alkanes	CCC	112	111·5	112	18	—	
	HCH	110	108	—			
Cyclopropane	HCH	116·5	118	118·2	23	5	10
Cyclobutane	HCH	113	112	114	21	3	7
Cycloheptane	HCH	110·5	109	—	18·5	0·5	1
Cyclohexane	CCC	112·5	112				
	HCH	110	108	—	18	0	0
Nortricyclene	θ	98·5	96	96·5	—	—	
	β_1	122	121	—			
	β_2	113	112	—			
Norcamphane	α_1	114	109·5				
	α_2	103	103*				
	α_3	91	92	—	—	—	
	β_1	106	108·5				
	β_2	112	107·5*				
	β_3	114	113*				

* Values of angles α_2, β_2, β_3 in ref. 2 were erroneous

energy due to the distortion of tetrahedral angles. It will be noted that the calculated values of the excess strain energy are substantially lower than the experimental (calorimetrical) ones. It follows that half of the strain is due to the change in the magnitude of the interaction energy of bonded atoms (bond strain).

The above examples show that the applied universal potential leads to reasonable results in the evaluation of many properties of compounds. Further study will enable us to make the interaction curves more precise. It seems, however, that this method of calculation to a precision substantially better than that of one order of magnitude is already worth considering.

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THE ELECTRONIC STRUCTURE OF SOME HETEROATOM CONJUGATED COMPOUNDS

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Abstract—Molecular orbital calculations have been carried out on some heteroatom and heterocyclic conjugated compounds. Parameters have been chosen for the coulomb and resonance integrals which lead, in general, to the correctly predicted values of dipole moments, bond lengths and chemical reactivity. The exceptions are azides, oxamide and tetrazole derivatives, and the discrepancies are discussed.

INTRODUCTION

THE simple molecular-orbital method has been shown by Orgel[1] to be a useful means of predicting the electric dipole moments and chemical reactivities in some conjugated heterocyclic compounds. Neglecting overlap, he obtained a set of parameters for the coulomb and resonance integrals which, in general, lead to differences between the predicted and experimental dipole moments of less than 0·3 D for a range of compounds from pyridine to benzoxazole. In all but one of the eighteen compounds considered, the heteroatom was situated within the ring structure, the exception being the "meso ionic" compound Sydnone which had a predicted moment much greater than the experimental value. More recently, Davies[2] has shown that the accuracy of the method is not improved by the inclusion of the overlap integrals.

The study reported here was undertaken with a view to extending the correlation to tetrazole and its derivatives, and to some heteroatom aliphatic compounds. As will appear later, this aim was only achieved in the case of the aliphatic compounds.

PARAMETERS

In the first instance calculations were made using the parameters given in Orgel's paper,[1] but these lead to wrongly predicted dipole moments in simple organic molecules such as ketones, aldehydes and amides. Values for β(CN), β(CO) and β(NO) were therefore adjusted against the dipole moments of cyanides, aldehydes and ketones, and nitromethane respectively. The final choice of parameters is

$$\alpha(\mathrm{C}) = \alpha;\ \alpha(-\mathrm{N}=) = \alpha + \beta;\ \alpha(-\overset{|}{\mathrm{N}}-) = \alpha + 2\beta;$$
$$\alpha(=\mathrm{O}) = \alpha + 2\beta;\ \alpha[\mathrm{C}(-\mathrm{X})] = \alpha + 0{\cdot}1\,\delta\mathrm{X};$$
$$\beta(\mathrm{CC}) = \beta;\ \beta(\mathrm{CN}) = \beta;\ \beta(\mathrm{CO}) = 1{\cdot}8\beta;$$
$$\beta(\mathrm{NN}) = \beta \text{ and } \beta(\mathrm{NO}) = 1{\cdot}2\beta.$$

These values are very similar to those used by Orgel *et al.*[1] and were chosen in preference to those proposed by Brown *et al.*[3,4], since their work was not primarily concerned with dipole moments and consequently their parameters have not been proven for this property.

[1] L. E. Orgel, T. L. Cottrell, W. Dick and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).
[2] D. W. Davies, *Trans. Faraday Soc.* **51**, 449 (1955).
[3] R. D. Brown and A. Penfold, *Trans. Faraday Soc.* **53**, 397 (1957).
[4] R. D. Brown and M. L. Heffernan, *Trans. Faraday Soc.* **54**, 757 (1958).

Following Orgel's work, the dipole moment was calculated by the vector addition of the π moment divided by 1·6 to the σ moment. In all cases the theoretical bond lengths were used and the bond angles taken to be 180°, 60° or those for regular hexagons or pentagons. σ bond moments were estimated using the following individual bond moments.

$$\overset{-}{C}-\overset{+}{H} = 0{\cdot}4\text{ D};\quad \overset{-}{N}-\overset{+}{H} = 1{\cdot}3\text{ D};\quad \overset{+}{C}-\overset{-}{N} = 0{\cdot}45\text{ D};\quad \overset{+}{C}-\overset{+}{O} = 0{\cdot}8\text{ D}$$

$$\overset{+}{N}-\overset{-}{O} = 0{\cdot}5\text{ D}$$

RESULTS

The results are given in Tables 1–3 and Figs. 1 and 2.

Table 1 lists the energies of occupied molecular orbitals [in terms of $(\alpha-\varepsilon)/\beta$] for each compound together with the delocalization energy and, in most cases, the resonance energy. β has been assigned many different values, but a rough value of −20 kcal/mole may be taken for comparative purposes.

TABLE 1. ENERGIES OF THE OCCUPIED MOLECULAR ORBITALS (E_1, E_2 ……)

Compound	E_1	E_2	E_3	E_4	E_5	Delocalization energy	Resonance energy
Alkyl cyanides	1·6466					4·3864 β	0·4 β
Ketones, aldehydes	3·1124					4·0248 β	0·4 β
Carbon dioxide	3·8683	2·0000				10·6732 β	2·6 β
Alkyl cyanates	3·4091	2·0000				8·8724 β	2·6 β
Amides						4·4362 β	0·4 β
Urea	3·6938	2·0000	2·0000			4·7876 β	0·8 β
Oxamide	3·7809	3·1351	2·0000	2·0000		9·0322 β	1·0 β
Glyoxal	3·4439	2·8804				8·2486 β	0·2 β
Azides	2·4142	1·0000				2·8284 β	
Diazomethane	2·2582	2·0000	0·5912			4·5988 β	0·6 β
Nitromethane	3·6971	2·0000				3·3942 β	
Nitrate ion	3·7321	2·0000				3·4642 β	
Guanidine	3·0000	2·0000	1·2808			3·0616 β	0·9 β
Nitroguanidine imino	3·9100	2·9590	2·0000	2·0000	1·4399	7·1378 β	
amino	4·0257	2·8962	2·0000	2·0000	1·3063	6·9564 β	
Dicyandiamide imino	3·0407	2·0599	2·0000	1·1529		8·7464 β	2·2 β
	2·0697	1·0000					
amino	3·1627	2·3173	1·5144	1·2367		9·5016 β	2·9 β
	2·0697	1·0000					
Pyrrole	2·9131	1·2643	0·7662			5·4872 β	1·5 β
Pyridine	2·3132	1·3188	1·0512			8·1664 β	2·1 β
Aniline	2·6578	1·7920	1·0000	0·8017		8·3030	2·3 β
Tetrazole 1							
1-Ethyltetrazole	3·2015	2·0000	1·3907			5·8844 β	1·7 β
1,5-Dimethyltetrazole							
Tetrazole 2							
2-Ethyltetrazole	3·2407	1·8330	1·4456			5·8386 β	1·6 β
1-Ethyl-5-ethylamino-tetrazole	3·3500	2·3698	2·0000	1·1654		6·2704 β	2·1 β
2-Methyl-5-methylamino-tetrazole	3·32075	2·5305	1·7532	1·1904		6·1897 β	2·0 β
1,3-Dimethyl-5-imino-tetrazole	3·4582	3·4222	1·8705	0·8635		7·3288 β	
1,4-Dimethyl-5-imino-tetrazole	3·4644	2·4142	1·8800	1·0000		7·6172 β	3·4 β

Fig. 1 contains diagrams of the electron densities on each atom, and the mobile bond order for each bond in all the non-cyclic structure studies. Comparison of the theoretical and experimental bond lengths[5] in these compounds is given underneath

[5] L. E. Sutton, *Tables of Interatomic Distances and Configuration in Molecules and Ions*. Special Publication No. 11 of the Chemical Society, London (1958).

the diagram of each molecule, the theoretical bond lengths being interpolated from graphs of single, double and triple covalent bond lengths[6] against mobile bond order. Although there is some doubt in defining pure C—N double bonds, bond lengths are relatively insensitive to changes in parameters and Coulson[7] has pointed out that the simplest molecular orbital method gives results which are as reliable as those given by the more refined treatments. Comparison of the predicted and observed dipole moments of the non-cyclic compounds is given in Table 2. Unless otherwise stated, the observed dipole moments have been taken from Wesson's compilation.[8]

Fig. 2 and Table 3 contain similar results for the cyclic compounds.

TABLE 2. PREDICTED AND EXPERIMENTAL DIPOLE MOMENTS OF SOME HETEROATOM CONJUGATED COMPOUNDS

Compound	π Moment calculated	σ Moment predicted	Total moment predicted	Total moment observed
Alkyl cyanides	4·5	0·85	3·7	3·6
Aldehydes, ketones	2·6	1·2	2·9	2·6–2·9
Alkyl amides	3·6	1·5	3·7	3·5
	$\theta = 76°$	$\theta = 75°$	$\theta = 76°$	
Urea	4·3	1·7	4·4	4·6
Alkyl azides	0·3	0·85	0·80	1·6
		$\theta = 60°$	$\theta = 72°$	
Diazomethane	1·2	0·85	1·6	1·4
Nitromethane	3·5	1·4	3·6	3·5
Nitroguanidine imino	11·2	1·8	8·3	7·0
	$\theta = -31·5°$	$\theta = -14°$	$\theta = -29°$	
amino	15·3	1·7	11·1	
	$\theta = -20°$	$\theta = -54°$	$\theta = -23°$	
Dicyandiamide imino	14·2	1·5	9·8	—
	$\theta = -40°$		$\theta = 34°$	
amino	8·8	1·0	6·0	—
	$\theta = 28°$	$\theta = 90°$	$\theta = 36°$	

θ is measured anticlockwise, relative to a $L \rightarrow R$ horizontal axis in the charge diagrams.

DISCUSSION

The discussion can be conveniently divided into two parts, the first dealing with the non-cyclic compounds, and the second with the cyclic ones.

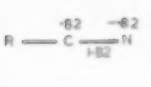
Non-cyclic molecules

Agreement between the predicted and experimental bond lengths (Fig. 1) and dipole moments (Table 2) is good. In general, it is within 0·02 Å for bond lengths and 0·2 D for dipole moments. However, there are a few exceptions which merit special comment, namely azides, oxamide, nitroguanidine and dicyandiamide.

Azides

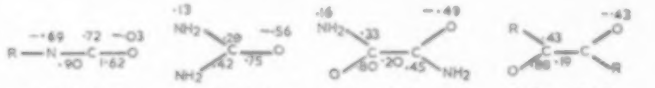
Although the theoretical bond lengths agree well with the experimental value, the predicted dipole moment is too small. Bonnemay and Daudel[9] have however shown

[6] G. W. Wheland, *Resonance in Organic Chemistry* p. 172. John Wiley, New York (1955).
[7] C. A. Coulson, *Theoretical Organic Chemistry* p. 54. Chemical Society Kekulé Symposium, Butterworths, London (1959).
[8] L. G. Wesson, *Tables of Electric Dipole Moments*. Technology Press, Massachusetts Institute of Technology (1948).
[9] A. Bonnemay and R. Daudel, *C.R. Acad. Sci., Paris* **230**, 2300 (1950).



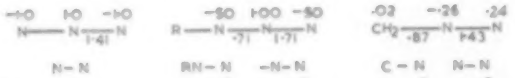
BOND LENGTH.		C–N	C–O	C–O	C–O	C–N
	THEORY	1·17 Å	1·22 Å	1·16 Å	1·24 Å	1·36 Å
	EXPT.	1·15 Å	1·23 Å	1·15 Å	1·22 Å	1·36 Å

ALKYL CYANIDES. ALDEHYDES. KETONES. CARBON DIOXIDE. AMIDES.



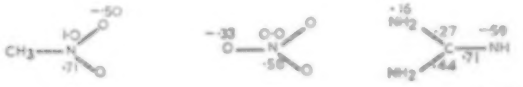
BOND LENGTH.		C–O	C–N	C–O	C–N	C–O	C–N	C–C	C–O	C–C
	THEORY	1·14 Å	1·27 Å	1·26 Å	1·37 Å	1·24 Å	1·37 Å	1·50 Å	1·23 Å	1·50 Å
	EXPT.	1·13 Å	1·21 Å	1·25 Å	1·37 Å	1·24 Å	1·32 Å	1·54 Å	1·23 Å	1·47–1·50 Å

ALKYL ISOCYANATES. UREA OXAMIDE GLYOXAL DIACETYL



BOND LENGTH.		N–N	RN–N	–N–N	C–N	N–N
	THEORY	1·16 Å	1·26 Å	1·12 Å	1·30 Å	1·14 Å
	EXPT.	1·16 Å	1·24 Å	1·10–1·14 Å	1·34 Å	1·19 Å

AZIDE ION ALKYL AZIDE DIAZOMETHANE



BOND LENGTH.		N–O	N–O	C–NH$_2$	C–NH
	THEORY	1·20 Å	1·23 Å	1·37 Å	1·32 Å
	EXPT.	1·21 Å	1·21 Å		

NITROMETHANE. NITRATE ION. GUANIDINE.

BOND LENGTH.		C–NH$_2$	C–N	N–N	N–O	C–NH$_2$	C–NH	C–NH–	N–N	N–O
	THEORY	1·36 Å	1·35 Å	1·29 Å	1·23 Å	1·37 Å	1·32 Å	1·38 Å	1·31 Å	1·22 Å
	EXPT.	1·36 Å	1·34 Å	1·35 Å	1·22 Å	1·36 Å	1·36 Å	1·34 Å	1·35 Å	1·22 Å
		IMINO FORM				AMINO FORM				

NITROGUANIDINE

BOND LENGTH.		C–NH$_2$	–C–N	–N–C–	–C–N	C–NH$_2$	C–NH	>C–NH	–NH–C	–C–N
	THEORY.	1·36 Å	1·34 Å	1·25 Å	1·21 Å	1·35 Å	1·37 Å	1·35 Å	1·27 Å	1·20 Å
	EXPT.	1·34–1·37 Å	1·36 Å	1·28 Å	1·22 Å	1·34 Å	1·37 Å	1·36 Å	1·29 Å	1·22 Å
		IMINO FORM				AMINO FORM.				

DICYANDIAMIDE

FIG. 1.

TABLE 3. PREDICTED AND EXPERIMENTAL DIPOLE MOMENTS IN SOME HETEROCYCLIC CONJUGATED COMPOUNDS

Compound	π Moment calculated	σ Moment predicted	Total moment predicted	Total moment observed
Tetrazole (1)*	4·7	1·8	4·8	5·1
	$\theta = 54°$	$\theta = 43°$	$\theta = 50°$	
(2)*	2·4	0·77	2·15	
	$\theta = 134°$	$\theta = 99°$	$\theta = 122°$	
1-Ethyltetrazole	4·7	1·4	4·4	5·5
1,5-Dimethyltetrazole	$\theta = 54°$	$\theta = 34°$	$\theta = 49°$	5·3
2-Ethyltetrazole	2·4	0·56	1·8	2·7
	$\theta = 134°$	$\theta = 64°$	$\theta = 118°$	
1-Ethyl-5-ethylamino-tetrazole†	5·6	1·6	5·1	7·4
	$\theta = 42°$	$\theta = 49°$	$\theta = 44°$	
	5·6	1·1	5·0	
	$\theta = 42°$	$\theta = 20°$	$\theta = 37°$	
5-Aminotetrazole (1)*	5·6	1·9	5·4	5·7
		$\theta = 42°$	$\theta = 42°$	
2-Methyl-5-methylamino-tetrazole†	1·6	0·9	1·9	2·55
	$\theta = 107°$	$\theta = 82°$	$\theta = 95°$	
1·3-Dimethyl-5-iminotetrazole	10·1	0·9	5·4	4·0
	$\theta = 110°$	$\theta = 276°$	$\theta = 112°$	
1·4-Dimethyl-5-iminotetrazole	4·5	−1·1	1·7	1·7
Pyrrole	2·0	0·3	1·6	1·8
Pyridine	2·3	0·85	2·3	2·2
Aniline	0·9	1·2	1·7	1·6

* Hydrogen in 1 or 2 position.
† σ moment depends on the stereochemistry of the 5-alkylamino group.
θ is measured anticlockwise relative to an upward vertical axis in the charge diagrams.

that a more complete treatment leads to accurately predicted bond lengths, and using their values for the electron densities, the π moment becomes 2·3 D giving a total predicted moment of 1·3 D, $\theta = 144°$ in good agreement with the experimental value of 1·6 D found in phenyl azide.

Oxamide

The bond lengths in oxamide[10,11] and other compounds of this general type, i.e. dithiooxamide,[12] oxalic acid,[13] and parabanic acid,[14] have been thoroughly examined and the central carbon–carbon bond length shown to be 1·5 Å, i.e. a pure single bond. Since all the compounds are planar or mainly planar and the bond angles at the carbon atoms consistent with trigonal hybridisation, complete delocalization over the entire σ bond structure (other than X—H bonds) would be expected, and calculations suggest that the carbon–carbon distance should be shortened by 0·05 Å. Poor agreement is also obtained for the carbon nitrogen bonds which are considerably shorter than the predicted value. If, however, the amino groups in oxamide are replaced by hydrogen (glyoxal), methyl groups (diacetyl) or chlorine (oxalyl chloride), the central

[10] E. M. Ayerst and J. R. C. Duke, *Acta Cryst.* **7**, 588 (1954).
[11] C. Romers, *Acta Cryst.* **6**, 429 (1953).
[12] B. Long, P. Markey and P. J. Wheatley, *Acta Cryst.* **7**, 140 (1954).
[13] K. G. Cox, M. W. Daugell and G. A. Jeffrey, *J. Chem. Soc.* 4854 (1952).
[14] D. R. Davies and J. J. Blum, *Nature, Lond.* **173**, 993 (1954): *Acta Cryst.* **8**, 129 (1955).

carbon–carbon bond distance is shortened by about 0·07 Å and agreement between experiment and theory is good (see Fig. 1). Similarly the corresponding carbon–carbon bond distances in the more complicated molecules dimethyl glyoxime, furoic acid, 6-carbomoyl 3 pyridazone and isatin lies between 1·44 Å and 1·49 Å. At first sight it might be thought that the phenomenon is caused by the repulsion of the adjacent positive charges of +0·33 electrons on the carbon atoms in oxamide. This is unlikely since the repulsive forces would be even greater in molecules of the glyoxal type where the adjacent charges are +0·43 electrons. Obviously important intramolecular forces must be acting between the heteroatoms in the oxamide type of molecules which are not present in the glyoxal type and which have not been included in the simple molecular orbital treatment. These forces probably involve hydrogen bonds, but the nature of the bonding is obscure and outside the scope of the present paper.

Nitroguanidine

Doubt existed for some time as to whether nitroguanidine existed in the imino or amino form, and the problem was only recently resolved by Richards and Yorke[15] who examined its nuclear magnetic resonance proton spectra and showed that the solid existed in the imino form. The theoretical bond lengths give a better fit with the experimental values[16] for the imino form, especially around the guanyl part of the molecular. In benzene solution, the reasonably close approach of the predicted dipole moment of the imino form (8·3 D) to the experiment moment (6·95 D),[17] and the greater delocalization energy of the imino form (7·1378 β) as compared with the amino form (6·9564 β) indicates the former structure to be more stable in solution.

Dicyandiamide

Whereas the imino structure is shown to be the more stable form of nitroguanidine, the amino form appears to be more stable in the case of dicyandiamide. The delocalization energy is greater for the amino form (9·5016 β) than the imino form (8·7464 β), and better agreement is obtained between the theoretical and experimental bond lengths[18] with the amino form. In the past it has been assumed[19] that difference in the terminal C—NH or C—NH_2 bond lengths was due to experimental error, but this does not appear to be so. No experimental dipole moment data is available for confirmatory purposes.

Cyclic molecules

In the molecular orbital calculations of heterocyclic nitrogen compounds the parameters chosen were those used by Orgel,[1] with the exception of β(CN) which was equated to β rather than 1·2 β. This change does not appear to alter the accuracy of the results for carbon-nitrogen heterocyclics. Calculations on pyridine and pyrrole lead to predicted dipole moments agreeing to within 0·1 D of the experimental value, and calculations on 1-ethyltetrazole and 2-ethyltetrazole using β(CN) = β and β(CN) = 1·2 β gave predicted dipole moments which did not differ by more than 0·05 D in each respective case. For aniline, the agreement between the predicted and

[15] R. E. Richards and R. W. Yorke, *Trans. Faraday Soc.* **54**, 321 (1958).
[16] J. H. Bryden, L. A. Burkardt, E. W. Hughes and J. Donohue, *Acta Cryst.* **9**, 573 (1956).
[17] W. D. Kumler and P. P. T. Sah, *J. Org. Chem.* **18**, 629 (1954).
[18] E. W. Hughes, *J. Amer. Chem. Soc.* **62**, 1258 (1940).
[19] Y. K. Syrkin and M. E. Dyatkina, *Structure of Molecules and the Chemical Bond* p. 184. Butterworths, London (1950).

experimental dipole moment shows that the chosen parameters are also valid for aromatic compounds containing an amino group attached to the ring structure.

In view of the good agreement between theory and experiment obtained both in Orgel's work and the present results, it was surprising to find that the predicted dipole moments of tetrazole or its derivatives, in general did not agree with the experimentally measured moments.[20,21] Even in those cases in which agreement appears to be good, i.e. tetrazole-1(H), 5-aminotetrazole-1(H) and 1,4-dimethyl 5-aminotetrazole, it is

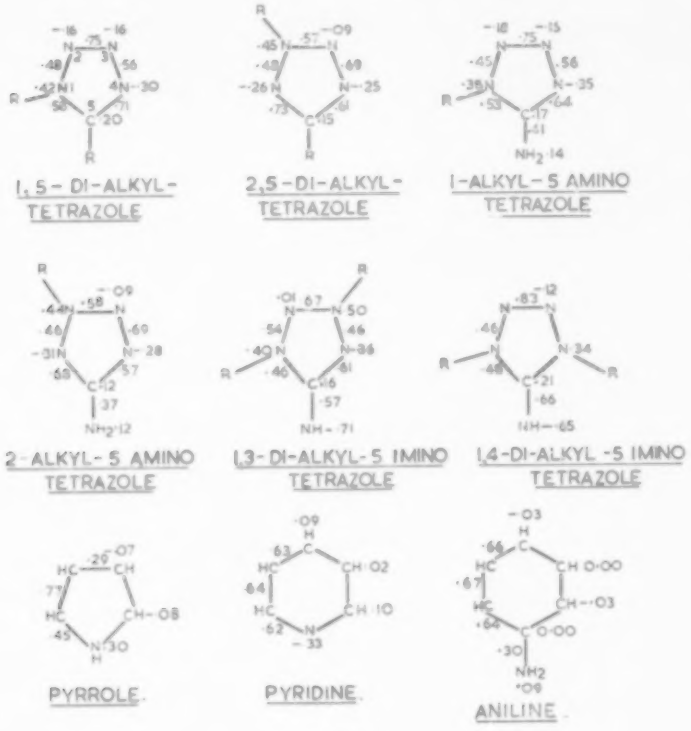

1, 5 - DI - ALKYL - TETRAZOLE
2,5 - DI - ALKYL - TETRAZOLE
1 - ALKYL - 5 AMINO TETRAZOLE
2 - ALKYL - 5 AMINO TETRAZOLE
1,3 - DI - ALKYL - 5 IMINO TETRAZOLE
1,4 - DI - ALKYL - 5 IMINO TETRAZOLE
PYRROLE.
PYRIDINE.
ANILINE.

FIG. 2.

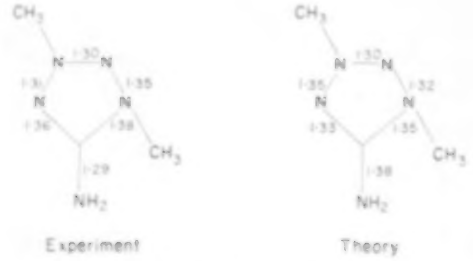
believed that the agreement is fortuitous. In tetrazole and 5 aminotetrazole both tautomerism and hydrogen bonding is possible. Problems arising in this way are usually resolved by studying the alkyl derivatives. Predicted values of the dipole moments of 1-ethyl- and 2-ethyl-tetrazole are 4·4 D and 1·8 D respectively and bear little resemblance to the experimentally measured values of 5·5 D and 2·7 D respectively. Replacing the ethyl groups by a hydrogen atom increases the predicted dipole moment by 0·4 D in each case, whereas the observed moment is 0·4 D *lower* than the value for 1-ethyltetrazole. The experimental values for tetrazole and 5-aminotetrazole were measured in dioxan[21] and the results of the present calculations suggest that these

[20] M. H. Kaufman, F. M. Ernsberger and W. S. McEwen, *J. Amer. Chem. Soc.* **78**, 4197 (1956).
[21] K. A. Jensen and A. Friediger, *Kgl. Danske Videnskab Selskab, Math-fys Medd.* **20**, No. 20, 1 (1943).

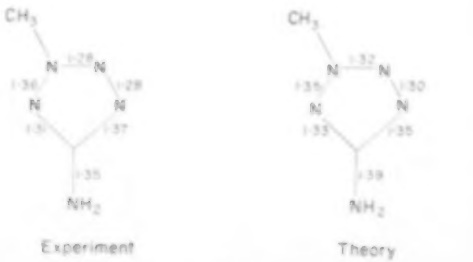
compounds in this solvent exist as tautomers. A simple calculation based on the experimental dipole moments indicates an approximate 70:30 ratio of the 1(H) to the 2(H) tautomers.

Attempts to clarify the situation by a study of the nuclear magnetic resonance proton spectra have not been successful.[22] Tetrazole is only sparingly soluble in dioxan and benzene and NMR peaks were only obtained in dimethyl formamide and in sulphuric acid. Unfortunately these solvents affect tetrazole chemically. In the proton accepting solvent dimethyl formamide, tetrazole dissociates, and the n.m.r. spectra shows only a single peak, apart from the solvent peaks, at −3·27 p.p.m. presumably due to the CH proton. Conversely, in 100 per cent sulphuric acid at least two or more of the tetrazole nitrogens would be protonated giving rise to further difficulties in interpretation of the spectrum.

Comparison of the bond lengths in the tetrazole derivatives is only possible in two



1,3-dimethyl-5-amino tetrazole



2-methyl-5-amino tetrazole

cases. With the meso ionic compounds 1·3 dimethyl 5-aminotetrazole[23] agreement is poor and the short C—NH_2 bond length found experimentally strongly suggests that the compound is in the imino (C—NH) form. In the other case 2-methyl 5-amino-tetrazole[20] agreement is good.

It is interesting to note that the simple molecular orbital theory predicts wrong dipole moments for azides as well as tetrazoles, and suggests that the values of β(NN) used in the calculations were inaccurate. However, calculations carried out using different values of β(NN) did not improve the agreement in the case of tetrazoles.

[22] R. G. Kidd and B. Figgis, Private communication (1960).
[23] J. H. Bryden, *Acta Cryst.* **8**, 211 (1955).

CONCLUSIONS

The simple molecular orbital theory leads to results which correctly predict the dipole moments, chemical reactivity and bond lengths in a large number of heterocyclic (see ref. 1) and heteroatom conjugated compounds. Tetrazole derivatives, tetrazole, azides and oxamide appear to be exceptions to the rule. In some cases hydrogen bonding may be the cause of the discrepancy.

Acknowledgements—The author wishes to thank Professor C. A. Coulson and Dr. L. E. Orgel for discussions on the tetrazole molecules. Thanks are also due to Dr. B. Figgis and Mr. R. G. Kidd, University College, London, who examined the NMR spectra of tetrazole.

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TURKISH TOBACCO—I

ISOLATION AND CHARACTERIZATION OF α- AND β-LEVANTENOLIDE

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R. J. Reynolds Tobacco Co., Winston-Salem, North Carolina

(*Received* 25 *November* 1960)

Abstract—Two hitherto unknown diterpene lactones have been isolated from Turkish tobacco. Characterization studies show that these compounds, now called α- and β-levantenolides, are represented by I and II. The levantenolides differ only in being epimeric at C_{12}, and are closely related to labdanolic acid.

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FRACTIONATION of the hexane extract of Turkish tobacco has yielded two lactones, α- and β-levantenolide,[1] belonging to the group of diterpenes typified by sclareol and labdanolic acid.

The infrared spectra (Figs. 1 and 2) of α-levantenolide (I) and β-levantenolide (II), $C_{20}H_{30}O_3$, were very similar, suggesting that the compounds were closely related.

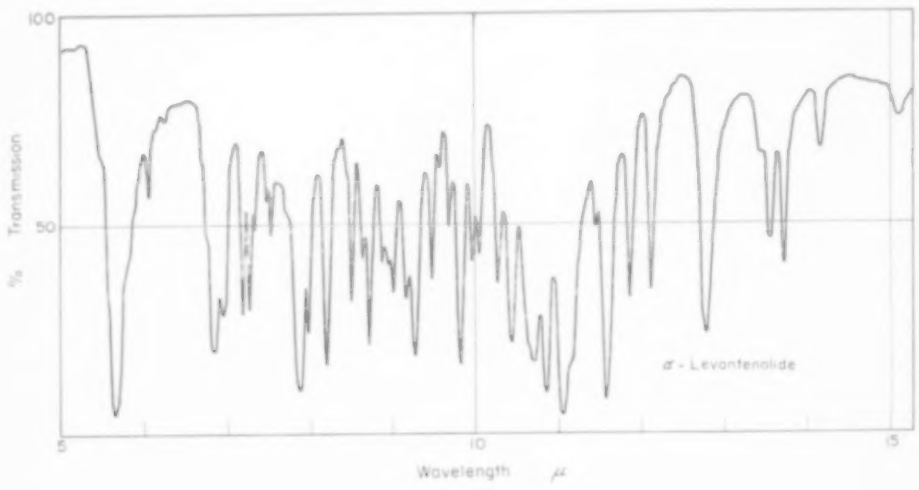


FIG. 1.

Absorption at 12·1 μ indicated the presence of the grouping $R_2C{=}CHR$. The carbonyl absorption at 5·75 μ suggested that both compounds are α,β-unsaturated γ-lactones.[2] The absence of hydroxyl or other carbonyl absorption required that the remaining oxygen be in an ether grouping. The NMR spectra[3] of the lactones were almost identical, showing one vinyl proton and five methyl groups, one of which is attached to a doubly-bound carbon beta to a carbonyl grouping. The partial structure,

[1] The name levantenolide was chosen to denote the functional groups as well as the fact that these lactones are found in tobacco commonly grown in the Near East.
[2] J. F. Grove and H. A. Willis, *J. Chem. Soc.* 877 (1951).
[3] Varian Associates, Palo Alto, California.

$RC(CH_3)$═CHC═O, then was apparent. The mass spectrum of α-levantenolide showed a parent mass of 318. Quantitative hydrogenation of the lactones gave equivalent weight values of 315, 309 and 277, indicating the presence of only one double bond.

The close relationship of α- and β-levantenolides was shown in several ways. Reduction of either lactone with lithium aluminum hydride gave the same triol, m.p. 145–146°. Reaction of either lactone with hydrazine provided the same pyridazone derivative (III), m.p. 212–213°. Saponification of either lactone followed by lactonization of the resultant acid gave predominantly α-levantenolide. Thus, any

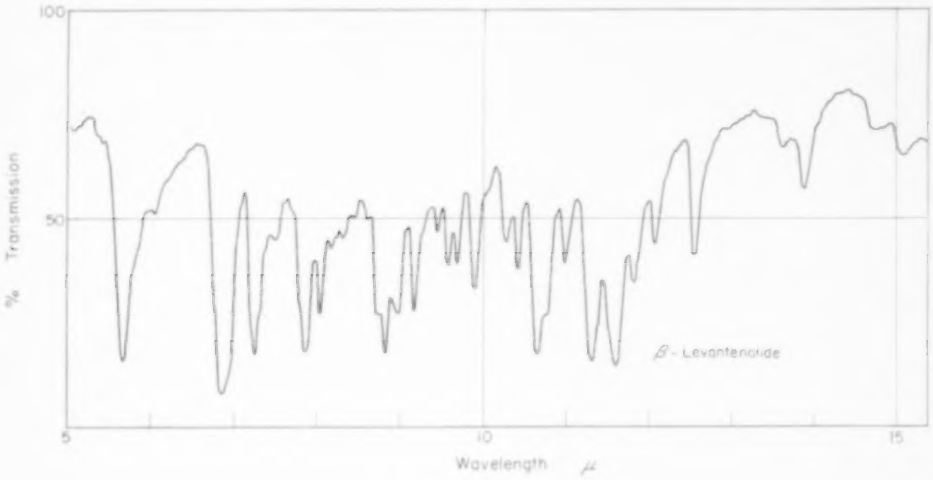


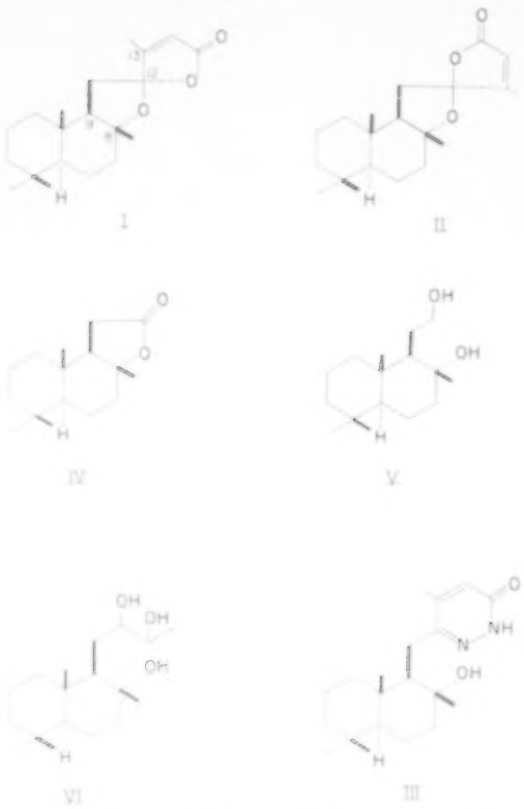
FIG. 2.

reaction which involves opening of the lactone rings will lead to a common product. *A priori*, α- and β-levantenolides can differ only in the configurations of the carbon atoms to which the lactone rings are attached. This facile interchange can occur only if the third oxygen atom is also attached to the carbon which changes configuration; i.e. α- and β-levantenolides must be the lactones of a hemi-ketal or a hemi-acetal. This conclusion is supported by the formation of a pyridazone upon reaction of the lactones with hydrazine.

Ozonization of α-levantenolide followed by oxidative hydrolysis of the ozonide with aqueous hydrogen peroxide led to the formation of the lactone (IV) and oxalic acid. The degradation to the lactone (IV)[4] provided a fragment of known constitution containing sixteen of the twenty carbon atoms. Oxalic acid provided the terminal carbon atoms which must include the lactone carbonyl group and one of the doubly-bound carbon atoms. The ozonolysis product has, therefore, undergone secondary cleavage. This is explained when it is understood that the ozonolysis product is an α-diketone which in turn is readily cleaved with hydrogen peroxide[5] or with ozone.

Ozonization of α-levantenolide was repeated. The ozonide was reduced with lithium aluminum hydride to give the diol (V), m.p. 132°, and the triol (VI), m.p.

[4] M. Stoll and M. Hinder, *Helv. Chim. Acta* **36**, 1984 (1953); M. Hinder and M. Stoll, *Ibid.* **36**, 1995 (1953).
[5] R. C. Fuson, *Advanced Organic Chemistry* p. 236. John Wiley, New York (1950).



I II IV V VI III

159·5–160·5°. Oxidation of the triol (VI) with lead tetraacetate gave acetaldehyde, isolated as the 2,4-dinitrophenylhydrazone in 75 per cent yield.

The saponification experiments have demonstrated that α-levantenolide is more stable than β-levantenolide, and indeed, it occurs to a greater extent in tobacco leaf. Construction of models shows that the formation of the lactone rings is sterically influenced by the methyl groups attached to carbons 8 and 13. This influence deters the 13-methyl group from assuming the position required for ring closure to give the lactone (II). Therefore, the structures I and II are proposed for α- and β-levantenolides respectively.

β-Levantenolide was converted via the dihydrolactone to the dihydropyridazone derivative. Treatment of the dihydropyridazone with potassium hydroxide under Wolff–Kishner conditions,[6] followed by esterification of the acidic products, gave methyl labdanolate,[7,8] m.p. 72–73°, and methyl 13-epilabdanolate,[7] m.p. 71–72°. Thus, α- and β-levantenolides are diterpenes of the class typified by sclareol,[9] manoöl,[10] labdanolic acid[7,8] and cativic acid.[11]

[6] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[7] S. Bory and E. Lederer, *Croat. Chem. Acta* **29**, 157 (1958).
[8] J. D. Cocker and T. G. Halsall, *J. Chem. Soc.* 4262 (1956).
[9] L. Ruzicka, C. F. Seidel and L. L. Engel, *Helv. Chim. Acta* **25**, 621 (1942); L. Ruzicka and M. M. Janot, *Ibid.* **14**, 645 (1931); J. A. Barltrop, D. B. Bigley and N. A. J. Rogers, *Chem. & Ind.* 400 (1959).
[10] J. R. Hosking and C. W. Brandt, *Ber. Dtsch. Chem. Ges.* **68**, 1311 (1935); J. R. Hosking, *Ibid.* **69**, 780 (1936).
[11] H. H. Zeiss and F. W. Grant, Jr., *J. Amer. Chem. Soc.* **79**, 1201 (1957).

EXPERIMENTAL

All melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. Elemental analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado. Active hydrogen analyses were performed in this laboratory by tritium exchange.[12]

Extraction of Turkish tobacco

One thousand pounds of aged, sun-cured Turkish tobacco, grown in Yugoslavia, were ground in a hammer mill to pass a ¼ in. screen. The tobacco was agitated and refluxed for 2 hr with 900 gallons of hexane, then 428 gallons of extract were siphoned off. Hexane (200 gallons) was added, then the mixture was agitated and refluxed for 0·5 hr and 436 gallons of extract were siphoned off. Hexane (445 gallons) was added, the mixture was agitated, and 645 gallons of extract were removed by water displacement. The total hexane extract was concentrated to 110 gallons, which contained 5·8 kg of solids, and extracted three times with 120 gallons of 9:1 methanol–water. Concentration of the combined aqueous methanol layers gave 2·8 kg of extract.

Fractionation of the extract

The aqueous methanol extract was chromatographed in 200 g portions using 5:1 Magnesol-Celite in a column 250 mm × 150 mm (dia.) and collecting the eluate, 15 l. of 1:1 hexane–ether, until a yellow band was about to be eluted. Concentration of the eluate from fourteen such columns gave 882 g of material which was fractionated by a second chromatogram using the same adsorbent. In chromatogram 2, the eluting solvents varied from 17:3 to 4:1 hexane–ether providing a separation into the following fractions:[13] Fraction 1, 158 g; Fraction 2, 142 g; Fraction 3, 185 g; and Fraction 4, 104 g.

On standing, Fraction 3 partially crystallized and 8·35 g of α-levantenolide (I) was removed by filtration. The filtrate was chromatographed on 5:1 Magnesol-Celite using hexane–ether mixtures of graded polarity. Appropriate fractions were partitioned between hexane and 90% methanol. Further partitioning of selected fractions using pentane and 4:1 methanol–water allowed separation of 0·73 g of β-levantenolide (II) and a further 0·3 g of α-levantenolide.

Crude β-levantenolide (4·7 g) crystallized from Fraction 4. The mother liquors were partitioned successively with hexane–90% methanol, hexane–70% methanol and pentane–70% methanol, and selected fractions were chromatographed on silicic acid. In this manner, an additional 1·3 g of β-levantenolide was obtained.

α-Levantenolide (I)

Recrystallization of the crude tobacco lactone from hexane gave α-levantenolide, m.p. 210°, $[\alpha]_D^{25}$ +60·4° ($CHCl_3$) (Found: C, 75·19; H, 9·32; Mol. wt. 318 (mass spectrometer). $C_{20}H_{30}O_3$ requires: C, 75·43; H, 9·58%; Mol. wt. 318).

Hydrogenation of α-levantenolide

Hydrogenation of 79·4 mg of α-levantenolide in ethanol over 30% Pd-C required 8·2 ml of hydrogen at 25° and 741 mm of Hg giving a value of 1·15 double bond. A second experiment gave a value of 1·03 double bond. Filtration of the mixture gave 85 mg of crude product. Recrystallization from hexane gave *α-levantanolide*, m.p. 144–146° (Found: C, 74·72; H, 10·13; Mol. wt. 320 (mass spectrometer). $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·01%; Mol. wt. 320).

β-Levantenolide (II)

The crude lactone isolated from Turkish tobacco was crystallized from hexane giving *β-levantenolide*, m.p. 208–209°, $[\alpha]_D^{25}$ −59·6° ($CHCl_3$) (Found: C, 75·33; H, 9·58. $C_{20}H_{30}O_3$ requires: C, 75·43; H, 9·58%).

Hydrogenation of β-levantenolide

Hydrogenation of 103 mg of β-levantenolide was accomplished over 30% Pd-C in ethanol with 8·2 ml of hydrogen at 24° and 736 mm of Hg giving a value of 1·01 double bond. Filtration and

[12] J. A. Giles, *Analyt. Chem.* **32**, 1716 (1960).
[13] The similarity of infrared spectra is used throughout the isolation as the criterion for grouping fractions.

concentration of the mixture gave 126 mg of crude product. Recrystallization from ethanol–hexane gave *β-levantanolide*, m.p. 192–194° (Found: C, 74·27; H, 10·02. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·01%).

Reduction of α-levantenolide with lithium aluminum hydride

Reduction of 50 mg of α-levantenolide was accomplished quantitatively according to Nystrom and Brown[14]. Recrystallization of the crude product from hexane-ethyl acetate gave *levanten-8α, 12,15-triol*, m.p. 145–146° (Found: C, 73·77; H, 11·43; Act. H, 0·97. $C_{20}H_{36}O_3$ requires: C, 74·02; H, 11·18; Act. H, 0·93%). Levanten-8α, 12,15-triol was also obtained by the similar reduction of *β*-levantenolide.

Reduction of α-levantanolide

Quantitative reduction of 83 mg of α-levantanolide according to Nystrom and Brown[14] gave *levantan-8α, 12,15-triol*, m.p. 121–122·5°, after recrystallization from hexane (Found: C, 73·14; H, 11·88. $C_{20}H_{38}O_3$ requires: C, 73·57; H, 11·73%). Levantan-8α, 12,15-triol was also obtained by catalytic hydrogenation of levanten-8α 12,15-triol.

Reaction of α-levantenolide with hydrazine

A mixture of 100 mg of α-levantenolide and 1 ml of 100% hydrazine hydrate in 1 ml of benzene was heated in a boiling water bath. After evaporation of the benzene, heating was continued for 4 hr. Evaporation of the mixture gave 107 mg of solid, m.p. 212–213°. The product was partitioned between ten layers of hexane and ten layers of 70% aqueous methanol. Methanol layers 1–2 yielded 96 mg of *3-(2′-hydroxy-2′,5′,5′,8′a-tetramethyldecahydronaphthalene-1)methyl-4-methyl-6-pyridazone*, m.p. 212–213°, λ_{max} 300, 315 mμ, λ_{min} 265 mμ, $\lambda_{infl.}$ 230 mμ (Found: C, 71·19; H, 9·34; N, 9·21. $C_{20}H_{32}N_2O_2$ requires: C, 72·25; H, 9·70; N, 8·43%). Attempts to recrystallize the pyridazone from several solvents resulted only in the formation of gels, thus preventing further purification. The same pyridazone was also obtained from the reaction of *β*-levantenolide and hydrazine.

Reaction of α-levantanolide with hydrazine

α-Levantanolide (539 mg) treated with hydrazine hydrate as described above gave 565 mg of crude product. Recrystallization from ethyl acetate gave *3-(2′-hydroxy-2′,5′,5′,8′a-tetramethyldeca-hydronapthalene-1)methyl-4-methyl-4,5-dihydro-6-pyridazone*, m.p. 206–207° (Found: C, 71·53; H, 10·19; N, 8·70. $C_{20}H_{34}N_2O_2$ requires: C, 71·81; H, 10·24; N, 8·38%). This same dihydropyridazone was also obtained by reaction of *β*-levantanolide with hydrazine hydrate.

Saponification and relactonization of β-levantenolide

A solution of 50 mg of *β*-levantenolide in 5 ml of methanolic 10% KOH was heated at reflux for five hours. The solution was diluted to 75 ml with water and carefully acidified to pH 4·0 with 1 N H_2SO_4. Extraction with ether gave 53 mg of a gummy acid. The acid was lactonized by heating at 105° for 68 hr. Examination of the infrared spectrum of the product showed that it was predominantly α-levantenolide containing some *β*-levantenolide.

The above experiment was repeated with α-levantenolide. The product was isolated and identified by its infrared spectrum as α-levantenolide.

Oxidation of α-levantenolide ozonide. Isolation of lactone (IV) *and oxalic acid*

A solution of 200 mg of α-levantenolide in 50 ml of ethyl acetate was cooled in an ice-salt bath. Ozonized oxygen was bubbled through the solution for 2·5 hr. The ozonide obtained after evaporation of the ethyl acetate was oxidized with 60 ml of 3% hydrogen peroxide.[13] The reaction mixture was separated into water-soluble and chloroform-soluble fractions.

The chloroform fraction was chromatographed on silicic acid with benzene and 49:1 benzene–ether to give 123 mg (78·5% yield) of the lactone (IV), m.p. 125–125·5°, $[\alpha]_D^{25}$ +46·5° (C = 1·9 in $CHCl_3$). Ruzicka[9] gives m.p. 123–124°, $[\alpha]_D^{25}$ +45·9° ($CHCl_3$). Identification was confirmed by

[14] R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.* **69**, 1197 (1947).
[13] C. S. Marvel, W. M. Schilling, D. J. Shields, C. Bluestein, O. R. Irvin, P. G. Sheth and J. Honig, *J. Org. Chem.* **16**, 838 (1951).

comparison of the infrared spectrum with that of the authentic lactone (IV) and by reduction with lithium aluminum hydride to the glycol,[4] m.p. 132–133°.

The water-soluble fraction was analyzed by paper chromatography with 3:1 phenol-1% formic acid.[16] A single spot, R_f 0·19, was observed in good agreement with oxalic acid.

Reduction of α-levantenolide ozonide. Isolation of the triol (VI)

Following ozonization of 204 mg of α-levantenolide in 50 ml of ethyl acetate at −10°, the ozonide in 20 ml of ether was reduced with 215 mg of lithium aluminum hydride.[13] Chromatography of the crude product on alumina with 19:1 chloroform–ethanol gave 88 mg. of the diol (V), m.p. 132°. Further elution with 9:1 chloroform–ethanol gave 84 mg of the triol (VI), m.p. 159·5–160·5° (Found: C, 71·99; H, 11·52; Act. H, 0·87. $C_{15}H_{34}O_3$ requires: C, 72·43; H, 11·48; Act. H, 1·01%).

Lead tetraacetate oxidation of the triol, m.p. 140–142°

A solution of 84 mg of the triol (VI) and 150 mg of lead tetraacetate in 10 ml of acetic acid was kept for 20 hr at 25°, then diluted with water and steam distilled. The distillate was collected in 100 ml of 2 N hydrochloric acid saturated with 2,4-dinitrophenylhydrazine. The resultant precipitate (47 mg), recrystallized from ethanol, gave acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 168–169°. The infrared spectrum was identical with that of an authentic sample.

Wolff–Kishner reduction of the dihydropyridazone

A solution of the crude dihydropyridazone (from 550 mg of β-levantenolide) and 296 mg of potassium hydroxide in 5 ml of diethylene glycol[6] was heated at 100° for three hours, then at 200–210° for 16 hr. The mixture was cooled, then partitioned using five 10% aqueous acetic acid and five aqueous lower layers, and ten benzene upper layers. Benzene layers 0–6 were concentrated and the residue esterified with excess diazomethane.[17] Chromatography of the methyl esters on silicic acid with benzene and 19:1 benzene–ether gave 178 mg of hydroxy ester, m.p. 57–59°. Using a second silicic acid column 105 mm × 45 mm (dia.), the hydroxy methyl ester was chromatographed with 49:1 benzene–ether and 100 ml fractions were collected. Fractions 40–47 gave 70 mg of solid, m.p. 69–72°. Two recrystallizations from petroleum ether gave methyl 13-epilabdanolate, m.p. 71–72°; Bory and Lederer[7] report m.p. 74–75°. The infrared spectrum was identical with that reported in the literature.[7] Fractions 53–59 gave 30 mg of solid, m.p. 65–69°. Two recrystallizations from petroleum ether gave methyl labdanolate, m.p. 72–73°. The melting point was undepressed on admixture with authentic methyl labdanolate isolated from gum labdanum.[18] The infrared spectra of the two specimens were identical.

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[16] J. B. Stark, A. E. Goodban and H. S. Owens, *Analyt. Chem.* **23**, 413 (1951).
[17] Th. J. DeBoer and H. J. Backer, *Org. Syn.* **36**, 16 (1956).
[18] J. D. Cocker, T. G. Halsall and A. Bowers, *J. Chem. Soc.* 4259 (1956).

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THE STRUCTURE OF AUREOTHIN, A NITRO COMPOUND OBTAINED FROM *STREPTOMYCES THIOLUTEUS*

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Abstract—The structure of aureothin, the third nitro compound obtained from nature, has been elucidated as I. Several reactions of aureothin and its derivatives are described.

AUREOTHIN, a by-product of the antibiotic aureothricin, is a yellow toxin isolated from the culture of *Streptomyces thioluteus*.[1] The structural studies have been carried out in our laboratory in the last few years and the results were reported in several communications. A summary of past studies together with some additional observations are reported herewith.[2]

Chemical nature and functional groups[3,4]

Aureothin (I), $C_{22}H_{23}O_6N$, m.p. 158°, forms yellow prisms soluble in methanol, ethanol, acetone, chloroform, and tetrahydrofuran, and insoluble in water and non-polar solvents; $[\alpha]_D^{15}$ 51° (in chloroform); λ_{max}^{EtOH} 257 mμ (log ε 4·39), 346 mμ (log ε 4·27); one methoxyl group (*Zeisel*); two —C—C(CH_3)— groups (modified method of Karrer[5]); no acetyl group. The ferric chloride reaction is negative, it is not acetylated, and an infra-red absorption around 3300 cm^{-1} is absent; thus it contains no hydroxyl group. On the other hand, a positive nitro group reaction and infra-red absorptions at 1505 and 1332 cm^{-1} suggest the presence of a nitro group.

Isomerization

When aureothin (I) is warmed in ethanolic mineral acids, the methoxyl group is easily demethylated to give desmethylisoaureothin (II), $C_{21}H_{21}O_6N$, yellow needles, m.p. 198°, pKa 4·6 (in 50% aqueous ethanol).[3,4] Methylation of II with diazomethane yielded an isomer of aureothin, isoaureothin (III), $C_{22}H_{23}O_6N$, m.p. 148°.[4] Acetylation of II with acetic anhydride and pyridine afforded the non-acidic acetate (IV), m.p. 182–184°, possessing an infra-red band of enol acetate at 1772 cm^{-1} (chloroform) or 1758 cm^{-1} (Nujol).[4] This was readily reconverted into the original compound (II) upon hydrolysis. Gradual addition of a dilute solution of diazomethane to II gave a mixture of aureothin (I) and isoaureothin (III),[6,7] and the action of dimethyl sulfate on the sodium salt of II gave aureothin (I) with a fairly good yield.[8] Hydrochloric acid

[1] K. Maeda, *J. Antibiotics* **A6**, 137 (1953).
[2] The chemistry of aureothin has recently been reviewed in Japanese. Y. Hirata and H. Nakata, *Jikken Kagaku Koza* Vol. 22, Chap. 16, Maruzen Company Ltd., Tokyo (1958).
[3] Y. Hirata, K. Okuhara and T. Naito, *Nature, Lond.* **173**, 1101 (1954).
[4] Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, *J. Chem. Soc. Japan* **78**, 1700 (1957).
[5] Y. Hirata, *J. Chem. Soc. Japan* **68**, 104 (1497).
[6] H. Nakata, S. Takahashi, K. Yamada and Y. Hirata, *Tetrahedron Letters* No. 16, 9 (1959).
[7] H. Nakata, *Bull. Chem. Soc. Japan* **33**, 1688 (1960).
[8] H. Nakata, *Bull. Chem. Soc. Japan* **33**, 1693 (1960).

treatment of isoaureothin (III) did not reconvert it into the desmethylisoaureothin (II).[4]

The carbonyl absorptions of I and II are at 1668 and 1682 cm^{-1} (chloroform), respectively, whereas those of the methylated III and the acetylated IV are at 1700 and 1710 cm^{-1}, respectively. These shifts show the presence of a hydrogen bonding in II. The marked difference between the carbonyl absorptions of I and III suggest that the carbonyl group is involved in the isomerization.

Oxidation

Oxidation of aureothin (I) with alkaline potassium permanganate and with chromic acid gave *p*-nitrobenzoic acid and *p*-nitro-α-methylcinnamaldehyde, respectively.[3,4] Ozonolysis of I produced formaldehyde and a small amount of methyl pyruvate in addition to *p*-nitrobenzaldehyde and *p*-nitro-α-methylcinnamaldehyde.[4] Identical results were obtained with isoaureothin (III) excepting that the yield of methyl pyruvate was considerably higher. Ozonolysis of tetrahydroaureothin derivatives does not give formaldehyde.

Reduction[4]

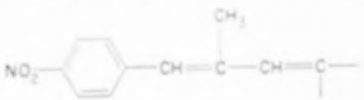
Reduction of I, II and III with ferrous salts or aluminium amalgam gave aureothamine (V), $C_{22}H_{25}O_4N$, m.p. 130–131°, desmethylisoaureothamine (VI), $C_{21}H_{23}O_4N$, m.p. 176–178°, and isoaureothamine (VII), $C_{22}H_{25}O_4N$, m.p. 134–136°, respectively, in which the nitro groups are reduced to amino groups. The Clemmensen reduction of I gave the hydrochloride of VI. Reduction of II with zinc, acetic anhydride and pyridine resulted in reduction of the nitro group and acetylation to afford N,O-diacetyl desmethylisoaureothamine, m.p. 211–212°. Isomerizations similar to these in the original nitro compound occurred readily when aureothamine (V) and N-acetyl aureothamine were treated with hydrochloric acid, and the products were desmethylisoaureothamine (VI) and its N-acetyl derivative, respectively.

When aureothin (I) and isoaureothin (III) were catalytically reduced in ethanol over platinum oxide, 5 moles of hydrogen were absorbed and the tetrahydro derivatives in which the nitro groups and two double bonds had been reduced were obtained. Tetrahydroaureothamine (VIII), $C_{22}H_{29}O_4N$, m.p. 137–138°, forms colourless plates.

Chromophores in aureothin and isoaureothin[5]

The above results suggest the partial structure (A) for aureothin and isoaureothin, and it is also apparent that the two compounds contain a carbonyl group which differs widely in its nature.

Synthetic model compounds were employed to check whether the chromophoric



(A)

group (A) was conjugated to this carbonyl group. The results are summarized in Tables 1 and 2.

If the *p*-nitrophenyl group is conjugated to the carbonyl group, the observed

[5] T. Naito, Y. Hirata, K. Okuhara and K. Iwadare, *J. Chem. Soc. Japan* **79**, 374 (1958).

Table 1. Ultra-violet spectra of synthetic model compounds

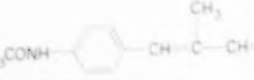
	Compound	m.p. (°C)	λ_{max}^{EtOH} (mμ)	log ε
(1)		116–117	301	4·29
(2)		141–143	323	4·33
(3)		116–118	327	4·32
(4)		135–137	355	4·35
(5)		178–180	359	4·34
(6)		131–133	262 377	4·14 4·31
(7)		46–47	221 311	4·06 4·09
(8)		86–88	243 340	4·20 4·24
(9)		82–83	271	4·27
(10)		84–86	304	4·47
(11)		123–125	268	4·25
(12)		123–125	296	4·50

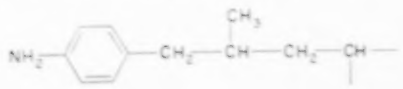
TABLE 2. ULTRA-VIOLET SPECTRA OF NATURAL COMPOUNDS

Compound	λ_{max}^{EtOH} (mμ)	log ε
(1) Nitro compounds:		
aureothin (I)	257	4·39
	346	4·27
desmethylisoaureothin (II)	248	4·26
	346	4·30
isoaureothin (III)	250	4·17
	335	4·19
O-acetyl desmethylisoaureothin (IV)	248	4·14
	335	4·23
(2) Amino derivatives:		
aureothamine (V)	241	4·24
	309	4·41
desmethylisoaureothamine (VI)	297	4·44
isoaureothamine (VII)	305	4·55
(3) N-Acetyl derivatives:		
N-acetyl aureothamine	300	4·63
N,O-diacetyl desmethylisoaureothamine	302	4·62
N-acetyl isoaureothamine	301	4·44
(4) Tetrahydro derivatives:		
tetrahydroaureothamine (VIII)	243	4·24
tetrahydroisoaureothamine	292	3·92

ultra-violet maximum would require three intervening double bonds, as in the compound (4) in Table 1. On the other hand, if it is not conjugated, then two double bonds would be required, as in (8). Models show that the maxima of the nitro compounds lie at shorter wavelength in comparison with the amino compounds when the nitrogenic chromophore is conjugated to the carbonyl group, e.g. (1) and (5), or (3) and (6). Since the natural compounds show the reverse tendency, it may be concluded that the p-nitrophenyl group is isolated from the carbonyl.

Subtraction of the ultra-violet absorption curves of these model compounds from those of the respective natural compounds gives the absorption spectra of the residual fragment containing the carbonyl group. The curves for this unknown chromophore have maxima at 250–260 mμ (log ε 4·0–4·1) and at 290–300 mμ (log ε 3·8–3·9), respectively, for aureothin and isoaureothin.

Similar subtractions of the absorption curves of *p*-toluidine and its derivatives from those of tetrahydroaureothamine (VIII) and its derivatives result in curves identical with those obtained above. This suggests that the conversion of (A) to the tetrahydroamino chromophore (B) is involved in the catalytic reduction and that the unknown chromophore remains intact (*vide infra*).

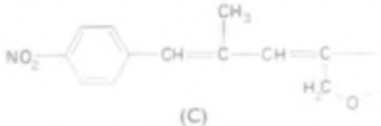


(B)

Ozonolysis of aureothin, isoaureothin, and their derivatives[10]

As was previously mentioned, the partial structure (A) for aureothin (I) and isoaureothin (III) was demonstrated by the production of *p*-nitro-α-methylcinnamaldehyde by ozonolysis. In order to identify the other structural units, ozonolyses of various derivatives were undertaken. The amino derivatives were converted to the acetates or benzoates prior to ozonolysis.

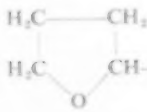
Formaldehyde is produced from aureothin (I) and isoaureothin (III) but not from the tetrahydro derivatives such as N-acetyl tetrahydroaureothamine, N-benzoyl tetrahydroaureothamine, and the corresponding iso-derivatives. The formaldehyde does not originate from a terminal methylene group since the number of $C—CH_3$ group remained constant before and after catalytic reduction, and since infra-red bands characteristic of terminal methylene group and gem-dimethyl group were undetectable in the curves of the original and reduced derivatives, respectively. Accordingly, it was presumed that the formaldehyde originated from the abnormal ozonolysis of an allylic ether system.[11] The position of the allylic double bond is indicated by the fact that the formaldehyde is not produced from the tetrahydro derivatives. Thus, the partial structure of aureothin may be expanded to the following:



(C)

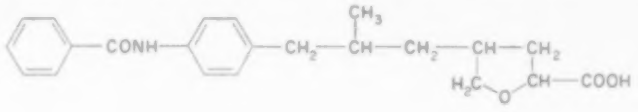
Ozonolysis of N-benzoyl tetrahydroaureothamine, m.p. 171–172°, gave a carboxylic acid (IX) with relatively high yields; *p*-bromo-phenacyl ester, $C_{21}H_{24}O_2N$-$COOCH_2COC_6H_4Br$-*p*, m.p. 145–146°. The infra-red bands of the carboxyl group of IX were at 1770 and 1723 cm^{-1} (monomeric and dimeric, respectively, in chloroform).

Table 3. Infra-red spectra of α-alkoxy acids

Compound	νC—O cm^{-1} ($CHCl_3$) monomer	dimer
$CH_3CH_2CH_2CH_2—O—CH_2COOH$	1780	1733
$CH_3CH_2—O—CH_2COOH$	1777	1733
$CH_3CH_2CH(O—CH_2CH_3)—COOH$	1766	1721
	1768	1723
N-Benzoyl aminotetrahydroaureothinic acid (IX)	1770	1723
Aureothinic acid (X)	1769	1721

[10] H. Nakata, Y. Hirata, K. Okuhara, K. Yamada, T. Naito and K. Iwadare, *J. Chem. Soc. Japan* **79**, 379 (1958).
[11] P. S. Bailey, *Chem. Rev.* **58**, 947 (1958).

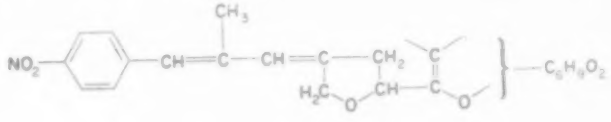
This high frequency suggested the preseence of an alpha-located electron attracting group, hence in the present case that of an ethereal function. This was confirmed by comparisons of infra-red spectra of several model compounds, as is shown in Table 3. The same behaviour of their *p*-bromophenacyl esters[12] also support the α-alkoxy acid structure. Taking into account the partial structure (C) and the fact that the acid (IX) possesses one C—CH_3 group, the above consideration leads to the following structure;



IX

The infra-red band of 1110 cm^{-1} is consistent with the presence of a tetrahydrofuran ring. This proves that, as previously mentioned, the double bonds reduced by the catalytic hydrogenation are those conjugated to the *p*-nitrophenyl group.

Furthermore since, the carboxylic acid is produced in fairly good yields only by ozonolysis, it is inferred that an enol ether linkage is present; thus, the structure of aureothin may be formulated as follows:

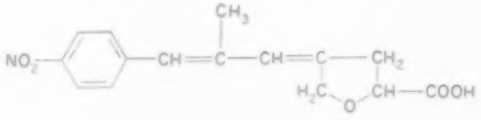


(D)

This structural unit is also common to isoaureothin since the same acid (IX) is obtained by the ozonolysis of N-benzoyl tetrahydroisoaureothamine, m.p. 165–166°.

Hydrogen peroxide oxidation of aureothin and isoaureothin[13]

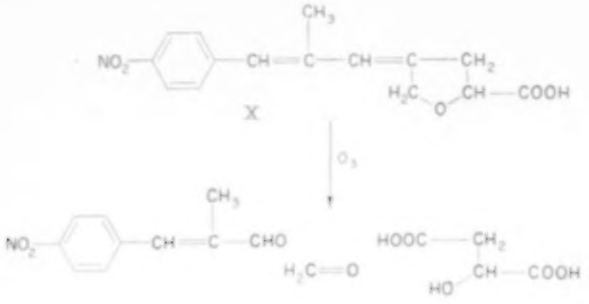
Oxidation of aureothin (I) and isoaureothin (III) with alkaline hydrogen peroxide gave aureothinic acid (X), $C_{15}H_{15}O_5N$, m.p. 147–149°. The ultra-violet absorption maximum of 249 mμ (log ε 4·14) and 345 mμ (log ε 4·20) showed that the partial structure (A) remained intact. The infra-red bands corresponding to the carboxyl group were at 1769 and 1721 cm^{-1} (monomeric and dimeric, respectively, in chloroform) or 1716 cm^{-1} (in KBr disk.) The methyl ester, m.p. 118–119°, exhibited two bands at 1758 and 1743 cm^{-1} in the ester carbonyl region in carbon tetrachloride solution. As in the case of the acid (IX), these spectroscopic properties suggested the presence of an α-ether linkage.[12] The acid (X) contains only a single C—CH_3 group and is optically active; this leads to the following structure:



X

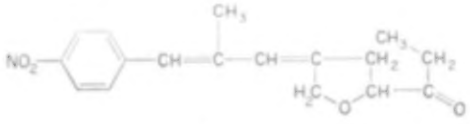
[12] H. Nakata, S. Matsuo and Y. Hirata, *Bull. Chem. Soc. Japan* **33**, 1458 (1960).
[13] Y. Hirata, H. Nakata and K. Yamada, *J. Chem. Soc. Japan* **79**, 390 (1958).

Ozonolysis of the acid gave *p*-nitro-α-methylcinnamaldehyde, formaldehyde, and malic acid (identified as its *p*-bromophenacyl ester). All of the carbon atoms may be accounted for by these three products, and accordingly, the structure (X) is rigorously confirmed. The production of formaldehyde and malic acid clearly indicated the abnormal ozonolysis of the allylic ether system in (X).



X

From the neutral fraction of the hydrogen peroxide oxidation product of aureothin, aureothinic ketone (XI) was isolated $C_{17}H_{19}O_4N$, m.p. 103–105°. Chromic acid oxidation yielded propionic acid. Thus, the structure is as follows:

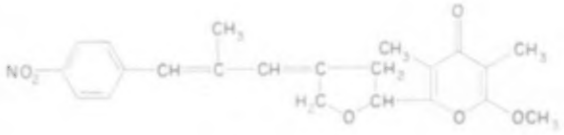


XI

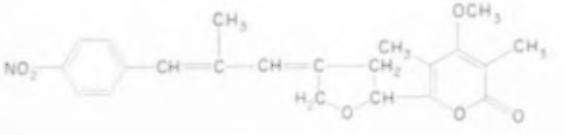
Alkaline degradation of aureothin and isoaureothin[11]

Decomposition of aureothin or isoaureothin with 1·5 N alkali under nitrogen yielded diethyl ketone as the volatile product. This showed the relative position of two methyl groups in the remaining part of the molecule.

The above results together with consideration of the partial structure (D) lead to the following structure (I) containing a γ-pyrone ring for aureothin and the alternative α-pyrone structure (III) for isoaureothin. Differentiation of the γ- and α-pyrone



I



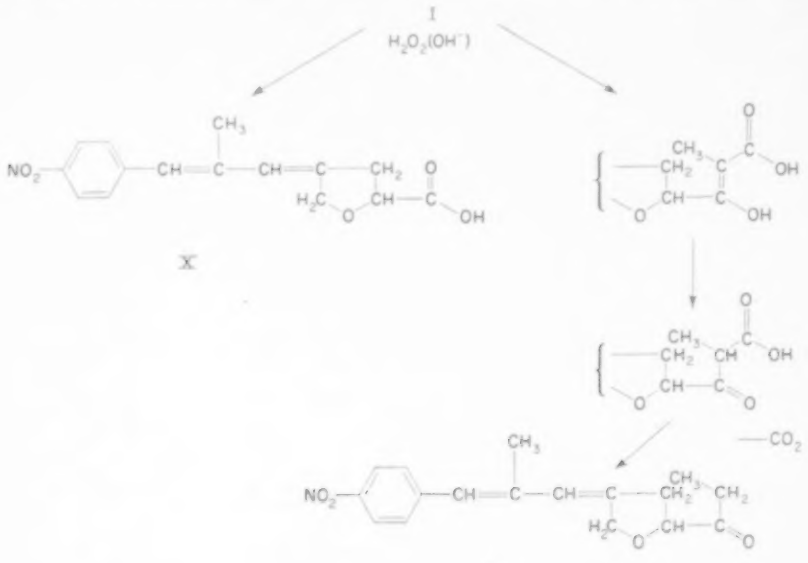
III

[11] K. Yamada, H. Nakata and Y. Hirata, *J. Chem. Soc. Japan* **81**, 340 (1960).

structure is based on comparisons of the ultra-violet and the infra-red absorptions of I and III with those of several model compounds.

A pyrone structure is suggested from indications of its aromaticity such as resistance to catalytic hydrogenation and from the subtracted ultra-violet curves (vide supra). The results of oxidation with hydrogen peroxide can also be explained satisfactorily.[13]

Taking into consideration the electron distribution in the γ-pyrone ring, the



X

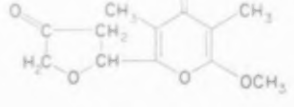
XI

production of a small amount of methyl pyruvate by ozonolysis of aureothin (I) is also explicable.[15]

Quantitative ozonolysis of aureothin and isoaureothin[14]

Confirmation of the structure I for aureothin and III for isoaureothin was given by the quantitative ozonization reactions.

Ozonolysis of aureothin (I) with 1 mole of ozone gave the previously known *p*-nitro-α-methylcinnamaldehyde and aureonone (XII), $C_{12}H_{14}O_5$, m.p. 153–155°. The ultra-violet absorption maximum of XII was 248 mμ (log ε 3·84) and 263 mμ (log ε 3·90), which was consistent with the γ-pyrone structure but not with the α-pyrone structure. The infra-red band of 1764 cm^{-1} (in chloroform) is ascribed to the carbonyl

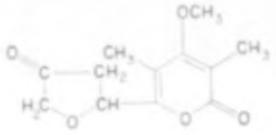


XII

[13] Ref. 11, p. 968.

group of tetrahydrofuran ring and two strong bands at 1666 and 1595 cm^{-1} are characteristic absorption of a γ-pyrone ring.

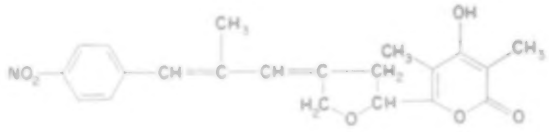
The corresponding derivative, isoaureonone (XIII), was also obtained from isoaureothin (III). The ultra-violet (λ_{max}^{EtOH} 294 mμ) and the infra-red ($\nu_{max}^{CHCl_3}$ 1764, 1704 1653 and 1567 cm^{-1}) absorptions were consistent with the γ-pyrone structure.



XIII

The structure of desmethylisoaureothin

As was previously mentioned, aureothin (I) is easily demethylated with mineral acids to give desmethylisoaureothin (II). Spectroscopic properties indicated the 4-hydroxy-γ-pyrone structure (II) for this demethylated product.[14]

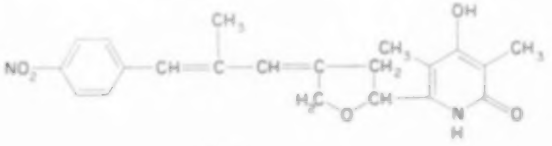


II

While the methylation of (II) with diazomethane under the usual condition gave isoaureothin (III) almost exclusively,[4] the same diazomethane methylation of II under certain specific experimental conditions gave an appreciable amount of aureothin (I).[6,7] On the other hand, the methylation of the sodium salt of II with dimethyl sulphate yielded a mixture of I and III.[8] These interconversions provided an additional and rigorous evidence of the structural relationships between aureothin (I) and isoaureothin (III).

Aza-derivatives of aureothin, isoaureothin and desmethylisoaureothin[16]

As expected for pyrone structures, the action of ammonia or of ammonium acetate in acetic acid on aureothin (I), desmethylisoaureothin (II), and isoaureothin (III) led to derivatives presumably containing pyridone rings. The reactions of I and of III were complicated and the results were inconsistent with the simple pyrone–pyridone transformation, but the product from II, aza-desmethylisoaureothin (XIV), $C_{21}H_{22}O_5N_2$, m.p. 238–239°, can be represented as follows:

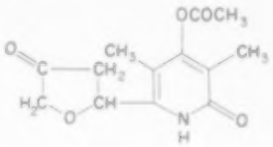


XIV

[16] K. Yamada, H. Nakata and Y. Hirata, *Bull. Chem. Soc. Japan* **33**, 1298 (1960).

The ultra-violet and the infra-red absorptions of XIV were in good agreement with synthetic pyridone derivatives.

Similar to aureonone (XII) and isoaureonone (XIII), ozonolysis of aza-desmethyl-

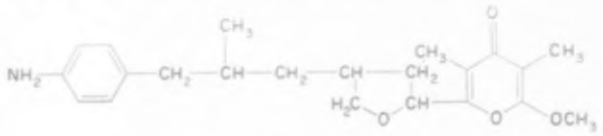


XV

isoaureothin acetate gave aza-desmethylisoaureonone acetate (XV), $C_{12}H_{15}O_5N$, m.p. 209–210°.

The structure of tetrahydroaureothamine[4]

Aureothin (I) and isoaureothin (III) both contain an asymmetric carbon atom, and are thus optically active. The tetrahydro derivative resulting from catalytic hydrogenation may accordingly be a mixture of several stereoisomers. Besides tetrahydroaureothamine (VIII), a considerable amount of an oil which can be isolated in a crystalline state only after conversion to a benzoyl derivative or a tartaric acid salt is



VIII

produced in the case of aureothin (I). The results with isoaureothin (III) were also rather complicated.

Reduction with complex metal hydride[17,18]

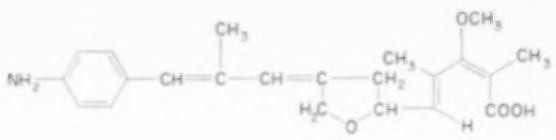
Reduction of isoaureothamine (VII) with lithium borohydride in tetrahydrofuran yielded an acidic substance, aminol H (XVI), $C_{22}H_{27}O_4N$, m.p. 156–158°. Since the carbonyl and methoxyl groups are still present in this compound, it follows that the acidic group should have originated from the reduction with the hydride reagent. An N,O-diacetyl derivative was obtained by acetylation of XVI under non-aqueous conditions (presence of water yielded N-acetyl aminol H). The infra-red band of N,O-diacetyl aminol H (1795 cm^{-1}, α,β-unsaturated acid anhydride, in Nujol) suggested that the acidity (p*K*a 6·1 in 50% aqueous ethanol) of XVI is due to a carboxyl group; a *p*-bromophenacyl ester, m.p. 85–87°, was obtained.

Aminol H (XVI) is still optically active, and the molecular formula shows an increase of two hydrogen atoms when compared with isoaureothamine (VII). Thus, structure (XVI) in which the α-pyrone ring of isoaureothamine has undergone a reductive cleavage is conceivable for aminol H.[19]

[17] K. Yamada, Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, *J. Chem. Soc. Japan* **79**, 384 (1958).

[18] K. Yamada, T. Naito, K. Okuhara, H. Nakata and Y. Hirata, *Bull. Chem. Soc. Japan*, **33**, 1303 (1960).

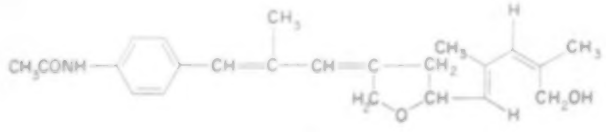
[19] As to the reduction with complex metal hydrides, the investigation, using simple α-pyrones, was carried out in our laboratory, and it was definitely established that a carboxylic acid like aminol H was invariably produced in each case.



XVI

In agreement with this formulation, the derivatives of aminol H show no infra-red absorption around 1575 cm^{-1} attributed to the α-pyrone ring. The structure is also consistent with the fact that more than one mole of methyl pyruvate is obtained by the ozonolysis of its O-methyl derivative (methyl ester).

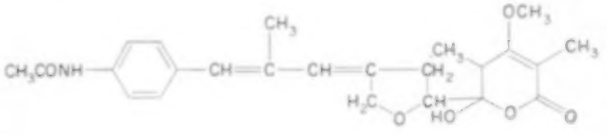
Reduction of N-acetyl O-methyl aminol H with lithium aluminium hydride in tetrahydrofuran results in the loss of the two methoxyl groups present in the starting material to give N-acetyl aminol A (XVII), $C_{23}H_{29}O_3N$, m.p. 155–156°.



XVII

Alkali-catalysed hydration of pyrone ring[18]

When N-acetyl isoaureothamine is heated in 3 N alkali, an acidic substance, was obtained lactol (XVIII), $C_{24}H_{29}O_6N$, m.p. 170–171°, optically inactive. Subtraction of the ultra-violet spectrum of the compound (12) of Table 1 from that of the lactol gave a curve, which showed a maximum at 248 mμ, indicating the destruction of the α-pyrone chromophore in XVIII. Treatment of this compound with acetic anhydride yielded a racemate of the original N-acetyl isoaureothamine. Examination of the infra-red spectra of XVIII and its sodium salt leads to the following structure:



XVIII

Other related natural products

Finally, we wish to emphasise the structural peculiarity of aureothin (I). The compound has a nitro group which is as yet a rather rare function in natural products. Only few other examples are known, including chloramphenicol,[20] hiptagenic acid,[21] azomycin,[22] and aristolochic acid.[23] Moreover, aureothin (I) has the substituted 2-methoxy-γ-pyrone structure. All other methylated 2,4-pyrononeS which have so far

[20] M. C. Rebstock, H. M. Crooks, Jr., J. Controulis and Q. R. Bartz, *J. Amer. Chem. Soc.* **71**, 2458 (1949).
[21] C. L. Carter and W. J. McChesney, *Nature, Lond.* **164**, 575 (1949).
[22] S. Nakamura, *Pharm. Bull.* **3**, 379 (1955).
[23] M. Pailer, L. Belohlav and E. Simonitsh, *Monatsh.* **87**, 249 (1956).

been found in nature are 4-methoxy-α-pyrones, such as yangonin,[24–28] anibine,[29,30] 4-methoxyparacotoin[29,31] and 5,6-dehydrokavain.[31]

EXPERIMENTAL

Melting points are uncorrected. Ultraviolet spectra were measured in ethanol unless stated otherwise.

Aureothin (I)

Yellow prisms, m.p. 158°. (Found: C, 66·85; H, 5·93; N, 3·43. $C_{22}H_{23}O_6N$ requires: C 66·49; H, 5·83; N, 3·52%). O-CH_3; 7·42% (0·95 mole). C—CH_3; 9·70% (2·57 moles), $\equiv C-\underset{\displaystyle CH_3}{\underset{|}{C}}=$; 21·98% (2·17 moles). $[\alpha]_D$ +51° ($CHCl_3$).

Desmethylisoaureothin (II)

(a) To a hot solution of aureothin (2 g) in ethanol (30 ml), was added 5 ml of conc HCl. After refluxing for 15 min, yellow crystals were formed. The reaction mixture was cooled, the crystals (1·8 g) were collected and washed with cold ethanol. Recrystallization from alcohol gave yellow needles of m.p. 196–198°.

(b) A suspension of aureothin (2·0 g) in 10% HCl (35 ml) was heated for 8 hr on a water bath, when the yellow colour of the crystals was changed to orange. The crystals were collected, washed with water and recrystallized from ethanol giving yellow needles (1·5 g), $[\alpha]_D^{16}$ +118° (ethanol). λ_{max} 248 mμ (log ε 4·26), 346 mμ (log ε 4·30). (Found: C, 65·72; H, 5·32; N, 3·70. $C_{21}H_{21}O_6N$ requires: C, 65·78; H, 5·52; N, 3·65%). C—CH_3; 10·58% (2·71 moles), $\equiv C-\underset{\displaystyle CH_2}{\underset{|}{C}}=$; 20·24% (1·94 moles).

In the usual acetylation with acetic anhydride and pyridine, an O-*acetyl derivative* of II was obtained as yellow needles (IV), m.p. 182–184 (recrystallization from ethanol). λ_{max} 248 mμ (log ε 4·14), 335 mμ (log ε 4·23). (Found: C, 64·96; H, 5·46; N, 3·42. $C_{23}H_{23}O_7N$ requires: C, 64·93; H, 5·45; N, 3·29%).

Isoaureothin (III)

To 1 g of II, 40 ml of ethereal diazomethane solution prepared from 5 g of nitrosomethylurea was added and the mixture was kept at room temp. overnight. The crystals (0·9 g) were collected, washed with a small amount of ether and recrystallized from alcohol. The m.p. was 148–149°, $[\alpha]_D^{16}$ +178° ($CHCl_3$). λ_{max} 250 mμ (log ε 4·17), 335 mμ (log ε 4·19). (Found: 66·71; H, 5·93; N, 3·28. $C_{22}H_{23}O_6N$ requires: C, 66·49; H, 5·83; N, 3·52%). C—CH_3; 9·52% (2·52 moles).

Oxidation with potassium permanganate

(a) To a stirred solution of II (0·5 g) in 0·5 N aq KOH (30 ml), was added a solution of 1·6% aq $KMnO_4$ at room temp under nitrogen till the purple color of permanganate was retained (65 ml, 5 moles). Carbon dioxide was identified. After filtration, the filtrate was acidified and extracted with ether. The ether solution was extracted with 0·1 N NaOH (10 ml). Neutralization of the alkaline solution gave a pale yellow precipitate which was purified by sublimation (180–200°) under reduced pressure, to give white crystals (50 mg), m.p. 234–235° (sealed tube). Methylation with diazomethane and recrystallization from methanol gave colourless crystals of the methyl ester, m.p. 92–93°, undepressed on admixture with an authentic sample of methyl *p*-nitrobenzoate. Oxidation with one mole of $KMnO_4$ gave only *p*-nitrobenzoic acid and the starting material II.

(b) To 2·9 g of I a solution of 3·2% aq $KMnO_4$ (50 ml, 1 mole) was added and the mixture was

[24] W. Borsche and C. K. Bodenstein, *Ber.* **62**, 2515 (1929).
[25] I. Chmielewska and J. Cieslak, *Roczniki Chem.* **28**, 38 (1954).
[26] I. Chmielewska, J. Cieslak, K. Gorczynska, B. Kontnik and K. Pitakowska, *Tetrahedron* **4**, 36 (1958).
[27] J. Cieslak, *Roczniki Chem.* **32**, 837 (1958).
[28] J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.* 502 (1960).
[29] W. B. Mors, O. R. Gottlieb and C. Djerassi, *J. Amer. Chem. Soc.* **79**, 4507 (1957).
[30] E. Ziegler and E. Nolken, *Monatsh.* **89**, 391 (1958).
[31] O. R. Gottlieb and W. B. Mors, *J. Org. Chem.* **24**, 17 (1959).

stirred for 24 hr at room temp under nitrogen. Carbon dioxide was identified as $BaCO_3$. After filtration of MnO_2 and the starting material, the filtrate was treated in the same manner as described in the case of (a), giving 70 mg of *p*-nitrobenzoic acid.

Chromic acid oxidation

To a solution of I (1·2 g) in glacial acetic acid a solution of chromic acid (150 mg) in glacial acetic acid was added at room temp. The mixture was diluted with twice its volume of water, extracted with chloroform and then the extract was washed with aqueous sodium carbonate. The solvent was removed under reduced pressure and the residue was chromatographed on alumina in benzene solution. Removal of the solvent from the fraction eluted with benzene furnished pale yellow needles, m.p. 108–110°. Recrystallization from methanol gave crystals of m.p. 111–113°, which showed no m.p. depression with synthetic *p*-nitro-α-methylcinnamaldehyde. Elution with benzene–acetone gave the starting material I (300 mg).

Ozonolysis of aureothin

Ozone was bubbled through a cooled solution of 1·0 g of aureothin in 15 ml of chloroform till the yellow colour disappeared (about 2 hr). The solvent was removed under reduced pressure, 5 ml of water was added to the ozonide, and CO_2-free air was bubbled through the mixture kept at 60° for about 2–3 hr. A relatively large amount of carbon dioxide was absorbed by aqueous barium hydroxide solution. From the aqueous layer, formaldehyde and methyl pyruvate were obtained as 2,4-dinitrophenylhydrazone, each of which was obtained by chromatographic separation (For further details concerning the formaldehyde and methyl pyruvate, see the heading on ozonolysis of aureothin and its derivatives). The oily material, separated from aqueous layer, was extracted with ether or benzene. On removal of the solvent under reduced pressure, a crystalline residue was obtained. Recrystallization from ethanol gave colourless needles, undepressed on admixture with the authentic sample of *p*-nitro-α-methylcinnamaldehyde.

Synthesis of p*-nitro-α-methylcinnamaldehyde*

Propionaldehyde (2·2 g, 2·7 ml) was added to a solution of *p*-nitrobenzaldehyde (5·5 g) in 50% aq ethanol (220 ml) and to this there was added dropwise, under stirring, an aqueous solution of sodium hydroxide (0·4 g in 10 ml of water) at room temp. After 30 min with occasional shaking, the precipitated crystalline product (m.p. 107–109°, yield about 5 g) was collected. Recrystallization from absolute alcohol raised the melting point to 112–114°, λ_{max} 297 mμ (log ε 4·30), (Found: C, 63·17; H, 4·91; N, 5·57. $C_{10}H_9O_3N$ requires: C, 62·82; H, 4·75; N, 7·33%).

Reduction of aureothin with $Fe(OH)_2$

A hot solution of 2·0 g of aureothin in 150 ml of alcohol was poured into a hot mixture of 20 g of $FeSO_4 \cdot 7H_2O$, 150 ml of water and 150 ml of conc aqueous ammonia, and the mixture was heated under reflux; the reaction mixture was left to cool at about 40°, and then extracted four times with 50 ml ether. The ethereal extract was dried over K_2CO_3 for a short time and concentrated under reduced pressure to give nearly colourless crystals of V (1·1 g), m.p. 128–129°. Recrystallization from ethanol raised the melting point to 130–131°, C—CH_3; 10·2% (2·5 moles), λ_{max} 241 mμ (log ε 4·24), 309 mμ (log ε 4·41), (Found: C, 72·11; H, 6·86; N, 3·91. $C_{22}H_{25}O_4N$ requires: C, 71·91; H, 6·86; N, 3·81%).

Acetylation of V in the usual way gave an N-*acetyl derivative*, m.p. 166–168°. Treatment with *p*-phenylazobenzoyl chloride under reflux in pyridine, gave yellow crystals, m.p. 227–229°.

Reduction of desmethylisoaureothin with $Fe(OH)_2$

To a hot mixture of $FeSO_4 \cdot 7H_2O$ (15 g), water (80 ml) and conc aqueous ammonia (80 ml), a hot solution of desmethylisoaureothin (1·0 g) in ethanol (100 ml) was added. The black ferric precipitate was filtered and the filtrate was acidified (pH, 4·5) with HCl and thus *desmethylisoaureothamine* (VI) was obtained in the form of its HCl-salt as a white precipitate (910 mg).

The diacetyl derivative of VI was obtained by the direct acetylation of the HCl salt of desmethylisoaureothamine with pyridine and acetic anhydride under reflux. Recrystallization from dioxane gave crystals of m.p. 214–215°, λ_{max} 301·5 mμ (log ε 4·62), (Found: C, 68·41; H, 6·31; N, 3·46. $C_{35}H_{27}O_6N$ requires: C, 68·63; H, 6·22; N, 3·20%).

Reduction of isoaureothin with $Fe(OH)_2$

A hot solution of III (4 g) in alcohol (200 ml) was poured into a hot mixture of $FeSO_4 \cdot 7H_2O$ (50 g), water (200 ml) and conc aqueous ammonia (150 ml) with stirring and the mixture was refluxed for 20 min. After cooling to about 40°, the reaction mixture was extracted three times with 150 ml ether. Upon removal of the solvent from this ether extract, under reduced pressure, white crystals (3·5 g) of *isoaureothamine* (VII) were obtained, which were recrystallized from ethanol, m.p. 134–136°, $[\alpha]_D^{29}$ +163° ($CHCl_3$), λ_{max} 305 mμ (log ε 4·55), (Found: C, 72·00; H, 6·90; N, 4·13. $C_{22}H_{25}O_4N$ requires: C, 71·91; H, 6·86; N, 3·81%), C—CH_3; 11·59% (2·84 moles), OCH_3; 8·27% (0·98 mole).

Acetylation of VII with acetic anhydride in pyridine at room temp gave N-acetyl isoaureothamine, m.p. 214–215°, $[\alpha]_D^{28}$ +140° ($CHCl_3$–CH_3OH), (Found: C, 70·25; H, 6·73; N, 3·97. $C_{24}H_{27}O_5N$ requires: C, 70·42; H, 6·65; N, 3·42%).

Reduction with aluminium amalgam

To a solution of 5 g of aureothin in 300 ml ethanol, aluminium amalgam and a small amount of water was added, and the mixture was stirred for 24 hr. Removal of the solvent under reduced pressure from the filtrate and hot alcoholic washings gave a product, which was extracted with ether. The ethereal solution was purified by chromatography on alumina and the eluted portion was evaporated to furnish crystals. Recrystallization from alcohol gave colourless crystals, m.p. 127–129°, undepressed on admixture with an authentic specimen of V.

Clemmensen reduction

A mixture of I (0·35 g), ethanol (10 ml), benzene (5 ml), amalgamated zinc and conc HCl (3 ml) was refluxed for 4 hr. The resulting white needles (0·2 g), filtered and washed with ethanol, had m.p. 210–215°. This compound was the hydrochloride of desmethylisoaureothamine, because its acetylation gave N,O-diacetyl desmethylisoaureothamine, which was obtained by the acetylation of VI.

Reductive acetylation

A mixture of II (130 mg), acetic anhydride (5 ml), two drops of pyridine and zinc was heated on a water-bath for 5 min. After filtration of the zinc, addition of water (50 ml) to the filtrate gave a white precipitate which gave crystals (110 mg), m.p. 216–218°, undepressed on admixture with an authentic sample of N,O-diacetyl desmethylisoaureothamine.

Isomerization of aureothamine

V (0·1 g), ethanol (5 ml) and conc HCl were heated on a water-bath for 15 min. The resulting white needles (0·06 g) filtered and washed with alcohol, had m.p. 210–214° (dec). Acetylation in the usual way gave N,O-diacetyl desmethylisoaureothamine.

Isomerization of N-acetyl aureothamine

To a solution of N-acetyl aureothamine (2·5 g) in ethanol (30 ml) ethanol (4 ml) and conc HCl (4 ml) were added, and the mixture was heated on a water-bath for 5 min. The resulting precipitate was filtered and crystallized from ethanol to give 2·0 g of colourless crystals, m.p. 217–220° (dec). Acetylation in the usual way gave N,O-diacetyl desmethylisoaureothamine.

Catalytic hydrogenation of aureothin

A suspension of 5·0 g of aureothin in 150 ml of warm alcohol was hydrogenated at room temp under atmospheric pressure of hydrogen in the presence of 500 mg of platinum oxide; after absorption of about 5 moles (ca. 1600–1750 ml) of hydrogen, the hydrogenation had practically ceased. The almost colourless filtrates were concentrated under reduced pressure in a stream of nitrogen and to the resultant oily material 10 ml of ether was added and it was allowed to stand for several days in an ice box. White crystals of *tetrahydroaureothamine* (VIII) were collected, and recrystallization from benzene gave colourless plates, m.p. 130–131°, λ_{max} 243 mμ (log ε 4·24), a shoulder at 276 mμ (log ε 3·94), (Found: C, 71·13; H, 7·90; N, 4·29. $C_{22}H_{29}O_4N$ requires: C, 71·13; H, 7·83; N, 3·77%), C—CH_3; 2·13 moles, $[\alpha]_D^{16}$ +36° ($CHCl_3$). The crystallized tetrahydroaureothmine was used for the preparation of benzoate A (m.p. 171–172°), benzoate B (m.p. 167–168°) and the residual

oily material was used for the preparation of benzoate C (m.p. 190–191°). Benzoate B was changed to benzoate D (m.p. 187–188°) on heating at 170°.

N-Benzoyl tetrahydroaureothamine (benzoate A)

To a solution of 600 mg of VIII in 7 ml of pyridine 300 mg of benzoyl chloride was added and the mixture was warmed at 80° for 10 min. The mixture was cooled below 0° and a small amount of crushed ice was added under cooling. The mixture was then poured into 50 ml of water and the precipitated white solid was collected and washed with water thoroughly (not with any dilute acid) and with a dilute solution of sodium carbonate and again with water, and recrystallized twice from ethanol; colourless or slight yellow pyramids, m.p. 171–172°, λ_{max} 271 mμ (log ε 4·17), (Found: C, 73·39; H, 7·11; N, 3·05. $C_{29}H_{33}O_5N$ requires: C, 73·24; H, 7·00; N, 2·95%), OCH_3; 6·53%. The substance gave a negative test for an aromatic amino group with *p*-N,N-dimethylaminobenzaldehyde, with ninhydrin and with 1,2-naphthoquinone-4-sulphonic acid.

When the same amine VIII was subjected to benzoylation under slightly more vigorous conditions than those employed in the preparation of benzoate A, the product having m.p. 167–168° (*benzoate B*) was obtained.

Catalytic hydrogenation of isoaureothin

Isoaureothin (3 g) was suspended in 180 ml of ethanol containing 300 mg of platinum oxide and hydrogenated at atmospheric pressure and room temp. The consumption of hydrogen ceased after 1100 ml (5·1 moles) had been taken up. The catalyst was separated by filtration and the colourless filtrate was concentrated under reduced pressure when an oily material was obtained. This oily product was kept in an ice box for a few weeks but no crystalline substance appeared. The oily product in ether-benzene was chromatographed on alumina, and concentration of the eluted fraction with benzene gave 2 g of a slightly yellow oily material.

A solution of 2 g of this oily material in 10 ml of pyridine was treated with 1 g of benzoyl chloride and kept at 80° for 20 min. After cooling the solution, it was poured onto 20 g of crushed ice. On allowing the resultant red-brown oily material to stand overnight at room temp, a crystalline substance appeared in the solidified mixture. Recrystallization from ethanol twice gave white needles of *N-benzoyl tetrahydroisoaureothamine* (600 mg), m.p. 165–166°, λ_{max} 280 mμ (log ε 4·27), $[\alpha]_D^{25}$ 0° (methanol), (Found: C, 73·24; H, 7·04. $C_{29}H_{33}O_5N$ requires: C, 73·24; H, 7·00%). Infra-red spectrum, 1692 (C=O and amide I), 1592, 1577, 1525 (sh), 1513 cm^{-1} (KBr). The optical inactivity does not mean that the compound was racemized, since the ozonolysis of this compound gave N-benzoyl aminotetrahydroaureothinic acid (IX) which had an optical activity. The concentration of mother liquor of crystalline N-benzoyl tetrahydroisoaureothamine led to a large amount of oily material, the infra-red spectrum of which was identical with that of the crystals.

Catalytic hydrogenation of desmethylisoaureothin

Desmethylisoaureothin was hydrogenated and the resultant tetrahydrodesmethylisoaureothin was benzoylated to give *benzoate E* (m.p. 167–168°) whose infrared spectrum was almost identical to those of benzoate B, C and D. Benzoate E was changed to benzoate F on heating at 107°. Recrystallization from alcohol gave colourless needles, m.p. 187–188°.

Synthetic model compounds for ultra-violet spectroscopic study

Syntheses of model compounds listed in Table 1 are described here.

(a) *5-(p-nitrophenyl)-4-methyl-2,4-pentadien-1-al.* To a solution of *p*-nitro-α-methylcinnamaldehyde (1 g, whose synthesis has been described in another part of this paper) and acetaldehyde (1 ml) in ethanol (50 ml), was added dropwise a 0·5% NaOH aq solution (30 ml) with vigorous stirring at room temp over a period of 20 min. The bright yellow precipitate was collected and recrystallized several times from alcohol to yield leaflets, m.p. 141–143°, (Found: C, 66·62; H, 5·10; N, 6·01. $C_{12}H_{11}O_3N$ requires: C, 66·35; H, 5·09; N, 6·45%).

(b) *6-(p-Nitrophenyl)-5-methyl-3,5-hexadien-2-one.* To a chilled solution of *p*-nitro-α-methylcinnamaldehyde (1 g) in acetone (30 ml), under stirring, 5 ml of 0·5% aq NaOH was added dropwise, when the solution became dark-coloured. After about 20 min at room temp, this was acidified with 5 ml of 1:3 aq HCl to give a bright yellow solution. A few minutes later, the solution was diluted

with water (60 ml), when a yellow crystalline precipitate appeared; this was recrystallized repeatedly from ethanol to give yellow needles (350 mg), m.p. 116–118°, (Found: C, 67·72; H, 5·87; N, 6·04. $C_{13}H_{13}O_3N$: requires: C, 67·52; H, 5·67; N, 6·08%).

(c) 8-(p-*Nitrophenyl*)-7-*methyl*-3,5,7-*octatrien*-2-*one*. This was synthesized by condensation of 5-(*p*-nitrophenyl)-4-methyl-2,4-pentadien-1-al with acetone under the same conditions as described in the case of (a), orange yellow crystal, m.p. 135–137°, (Found: C, 70·09; H, 5·95; N, 5·43. $C_{15}H_{15}O_3N$ requires: C, 70·02; H, 5·88; N, 5·44%).

(d) p-*Amino*-α-*methylcinnamaldehyde*. A hot solution of 300 mg of *p*-nitro-α-methylcinnamaldehyde in 15 ml of ethanol was added with stirring to a hot mixture of $FeSO_4 \cdot 7H_2O$ (5 g), water (20 ml) and conc aq ammonia (10 ml). After 10 min at 80°, the reaction mixture was extracted with ether. The ether solution, after drying with K_2CO_3, was evaporated under reduced pressure and crystals were obtained. Recrystallization from ethanol gave orange yellow needles, m.p. 178–180°, (Found: C, 74·59; H, 6·98; N, 8·80. $C_{10}H_{11}ON$ requires: C, 74·51; H, 6·88; N, 8·69%).

(e) 6-(p-*Aminophenyl*)-5-*methyl*-3,5-*hexadien*-2-*one*. The nitro compound, the synthesis of which was described in (b), was treated with $FeSO_4 \cdot 7H_2O$–aq NH_3 in the same manner as described in (d), m.p. 132–133°, (Found: C, 77·51; H, 7·41; N, 7·14. $C_{13}H_{15}ON$ requires: C, 77·58; H, 7·51; N, 6·96%).

(f) p-*Nitro*-α-*methylcinnamyl alcohol*. A solution of 500 mg of *p*-nitro-α-methylcinnamaldehyde in 20 ml of ethanol was treated with $NaBH_4$ (50 mg) in 20 ml of ethanol, and refluxed for 20 min. After cooling, the solution was neutralized (pH 7) with dilute HCl, and extracted with ether. The ether extract was evaporated under reduced pressure and an orange yellow oil remained which crystallized after placing in an ice box, m.p. 46–47°.

(g) 6-(p-*Nitrophenyl*)-5-*methyl*-3,5-*hexadien*-2-*ol*. To a solution of 350 mg of the nitro-ketone compound, described in (b), in tetrahydrofuran (10 ml) 50 ml of $LiBH_4$ was added and the mixture was kept at room temp for 20 min. After addition of water (5 ml), the solvent was removed and a red-brown oil was obtained, which became solid. Upon recrystallization from ethanol, yellow needles appeared (200 mg), m.p. 86–88°, (Found: C, 67·38; H, 6·26; N, 6·41. $C_{13}H_{15}O_3N$ requires: C, 66·93; H, 6·48; N, 6·01%).

(h) p-*Amino*-α-*methylcinnamyl alcohol*. The nitro-alcohol, described in (f) and obtained from 500 mg of *p*-nitro-α-methylcinnamaldehyde, in ethanol (15 ml) was poured into the mixture of $FeSO_4 \cdot 7H_2O$ (5 g), water (15 ml) and conc aq ammonia (10 ml) and the resultant mixture was heated for 15 min. The mixture was filtered and the filtrate was extracted with ether. The ether extract was concentrated under reduced pressure to give crystals. Recrystallization from water gave colourless crystals (80 mg), m.p. 82–83°.

This amino alcohol was treated with acetic acid–acetic anhydride (2:1) at room temp for 10 min and then water was added. The resultant white precipitate was recrystallized from water to give p-*acetylamino*-α-*methylcinnamyl alcohol*, m.p. 123–125°.

(i) 6-(p-*Aminophenyl*)-5-*methyl*-3,5-*hexadien*-2-*ol*. To a solution of 150 mg of the corresponding nitro alcohol described in (g) a mixture of $FeSO_4 \cdot 7H_2O$ (2 g), water (75 ml) and conc aq ammonia (10 ml) was added. The mixture was heated for 10 min and extracted with ether, and the resultant ether extract was evaporated under reduced pressure to give an oily material. Ligroin (30 ml) was added to this oily product and heated. After the insoluble part was removed, the ligroin solution was cooled to give slightly yellow crystals, which upon recrystallization from ligroin gave needles (40 mg), m.p. 84–86°, (Found: C, 76·01; H, 8·13; N, 6·76. $C_{13}H_{17}ON$ requires: C, 76·81; H, 8·43; N, 6·89%).

Acetylation of this compound under the same condition shown in the case of (h) gave N-*acetyl derivative*, m.p. 123–125°.

Analysis of C—CH_3

The determination of the C—CH_3 group was carried out by the Kuhn–Roth method. On distilling the mixture three or four times, the volatile acids produced on oxidation, were almost entirely in the distillates. In the case of the *p*-nitroaromatic compound, however, the distillate, obtained after the repeated distillation (nine times) of the oxidized product, was still acidic and consumed a small amount of alkali. This was due to the fact that *p*-nitrobenzoic acid, produced by oxidation, was gradually distilled out. This was confirmed by an experiment using authentic *p*-nitrobenzoic acid.

In the present case, the distillations were repeated seven times, and the amount of alkali consumption observed was corrected for the co-existence of *p*-nitrobenzoic acid in the distillates, on the basis of the following data.

Table 4. Consumption of alkali due to *p*-nitrobenzoic acid (distillations were repeated seven times)

p-Nitrobenzoic acid (mg)	Consumption of alkali (ml) N/100 NaOH (f 1·07)	Consumption of alkali per 1 mg *p*-nitrobenzoic acid (ml)	
		obs.	mean
4·069	0·572	0·145	0·155
1·853	0·362	0·195	
4·475	0·557	0·124	

Ozonolysis of aureothin and its derivatives

Ozonolysis of aureothin and its derivatives was carried out as follows.

Ozone was bubbled through the cooled chloroform solution for about 2–3 hr, until the absorption of ozone practically ceased. The solvent was removed and the resultant ozonide was decomposed by warming at 60° with 10 ml of water. Carbon dioxide was trapped by aqueous barium hydroxide solution (0·5–1 mole as $BaCO_3$), and a small amount of volatile carbonyl compounds was caught by a 2 N HCl solution of 2,4-dinitrophenylhydrazine. An oily product was separated from the aqueous layer and washed with water several times. This oily product soon solidified and was recrystallized from alcohol to give crystals of *p*-nitro-α-methylcinnamaldehyde (*vide supra*).

Addition of a 2,4-dinitrophenylhydrazine solution (2 N HCl) to the combined solution of the aqueous layer and the washings gave a mixture of hydrazones. The dried mixture of the hydrazones was extracted with hot benzene, and the benzene solution was chromatographed on alumina to separate each component. Sometimes by cooling the benzene extract, crystals (most of them were the 2,4-dinitrophenylhydrazone of methyl pyruvate) were separated. (In the case where ozonization had given formaldehyde, 2,4-dinitrophenylhydrazone of formaldehyde was eluted as the first fraction by chromatography on alumina. The solvent was removed and the residue was recrystallized from alcohol to give yellow needles, m.p. 156–158°, undepressed on admixture with authentic sample of 2,4-dinitrophenylhydrazone of formaldehyde.)

There were two kinds of 2,4-dinitrophenylhydrazones of methyl pyruvate and both of them were obtained by ozonolysis. These two hydrazones were separated by chromatographic techniques as a yellow band and a brown band.

The two kinds of 2,4-dinitrophenylhydrazones are as follows.

Form I: yellow orange needles, m.p. 179–180° (To methanol containing H_2SO_4, pyruvic acid and 2,4-dinitrophenylhydrazine was added and then the mixture was heated).

Form II: yellow prisms, m.p. 147–148° (2,4-dinitrophenylhydrazine solution was added to methyl pyruvate).

The yields of the products from various derivatives are listed in Table 5.

Ozonolysis of N-benzoyl tetrahydroaureothamine

Through a cooled solution (0°–10°) of 515 mg of N-benzoyl tetrahydroaureothamine in 10 ml of chloroform ozone was bubbled until about two equivalents of ozone were consumed (which was determined by techniques modified from gas analysis). After the removal of the solvent under reduced pressure, the ozonide was decomposed by adding 10 ml of water, and CO_2-free nitrogen gas was bubbled through the warmed mixture (60°) for 1 hr. The aqueous layer was separated from the oily material and treatment of this aqueous layer with 2,4-dinitrophenylhydrazine solution gave about 40 mg of hydrazone mixture, from which two kinds of yellow hydrazones (A and B, for convenience) were separated by chromatographic techniques. "A" was again chromatographed on alumina and was characterized as the form II of 2,4-dinitrophenylhydrazone of methyl pyruvate,

yellow needles, m.p. 179–180°, undepressed by admixture with an authentic sample. Another B was recrystallized from ligroin–benzene (5:1), bright yellow prisms, m.p. 144–145°, undepressed on admixture with an authentic sample of form I of 2,4-dinitrophenylhydrazone of methyl pyruvate.

TABLE 5. YIELDS OF THE PRODUCTS BY OZONOLYSIS

Compound	Formaldehyde (equiv. mole)	Methyl pyruvate (equiv. mole)
Aureothin	0·19	0·01–0·02
Isoaureothin	0·12	0·19
N-Acetyl tetrahydroaureothamine	—	trace
N-Acetyl tetrahydroisoaureothamine	—	ca. 0·1
N-Benzoyl tetrahydroisoaureothamine	—	0·15
N-Acetyl isoaureothamine	trace	0·21
N-Acetyl aminol H	—	0·22
N-Acetyl O-methyl aminol H	—	1·05

The fraction (oil) insoluble in water was dissolved in ether which was shaken with conc aq $NaHCO_3$ solution. After the sodium bicarbonate solution was left for some time, white crystals precipitated, the sodium salt of N-benzoyl amino tetrahydroaureothinic acid (IX), 120 mg. The ether layer was washed with water several times, dried with anhydrous sodium sulphate and concentrated. The resultant colourless oily substance which was chromatographed on alumina in ethereal solution showed an infra-red band of γ-lactone at 1772 cm^{-1} and was shown to be identical with the neutral oily product obtained by the ozonolysis of N-benzoyl tetrahydroisoaureothamine, λ_{max} 272 mμ (*cf.* N-benzoyl *p*-toluidine, λ_{max} 271 mμ), $[\alpha]_D^{28}$ +39 ± 3° (CH_3OH).

N-*Benzoyl aminotetrahydroaureothinic acid* (IX)

The sodium salt, thus obtained was rather insoluble in water and soluble in methanol and ethanol, infra-red spectrum, 1598 cm^{-1} (KBr, carboxylate).

For the purpose of the isolation of free IX, an aqueous methanol solution of the sodium salt was acidified with dil HCl, giving only an oily material. However, by adding water to the solution of the sodium salt in pyridine–acetic anhydride, colourless crystals were obtained, m.p. 83–86°. The methanolic solution containing 30 mg of sodium salt of IX and 50 mg of *p*-bromophenacyl bromide was refluxed for 1 hr. Water was added to the warm solution until the solution became slightly turbid. After cooling, 25 mg of *p-bromophenacyl ester* of IX precipitated gradually. This was collected and dried. Recrystallization from ethanol–water gave plates, m.p. 145–146°, (Found: C, 63·59; H, 5·43; N, 2·41; Br, 14·20. $C_{30}H_{30}O_5NBr$ requires: C, 63·83; H, 5·36; N, 2·48; Br, 14·17%), C—CH_3, 2·16% (0·87 mole), $[\alpha]_D^{28}$ +23° (CH_3OH).

The ozonolysis of N-benzoyl tetrahydroisoaureothamine by the same method gave a sodium salt. The *p*-bromophenacyl ester had m.p. 145–146°, undepressed by admixture with the ester of IX.

Synthesis of α-alkoxy carboxylic acid and ester

These compounds were synthesized to use as model compounds for infra-red spectra. The details have been reported.[12]

Aureothinic acid (X)

To a stirred solution of 2 g of I in 50 ml ethanol, 2 g of KOH in 10 ml ethanol and hydrogen peroxide (30%), were added alternately.

The yellow solution turned brown on addition of excess KOH solution, and became yellow again on addition of hydrogen peroxide solution. The mixture was kept orange during the reaction by adjusting the addition of the reagents. The addition of hydrogen peroxide was continued till the crystals of I disappeared and a white inorganic substance appeared. About 1·5–2·0 g of KOH and 5–6 ml of hydrogen peroxide (30%) were added for 8 hr. Excess water was added to the reaction mixture which became clear. The solution was acidified with 6 N HCl. The acidic aqueous solution

was extracted with ether three times. The ether extract was shaken with conc sodium bicarbonate solution four times, when aureothinic acid (X) was extracted with sodium bicarbonate solution and a neutral substance, *aureothinic ketone* (XI) remained in the ether layer. The sodium bicarbonate solution was acidified, and then extracted with ether three times. The ethereal layer thus obtained, after shaking with water, was concentrated under reduced pressure. The residue was cooled in the refrigerator and the slightly yellow crystals were filtered and recrystallization from ethanol gave the crystals of X, m.p. 149–151°, yield 0·2 g, λ_{max} 249 mμ (log ε 4·14), 345 mμ (log ε 4·20), $[\alpha]_D^{28}$ +54° (CH_3OH), (Found: C, 62·31; H, 5·29; N, 4·89. $C_{15}H_{15}O_5N$ requires: C, 62·28; H, 5·23; N, 4·84%), C—CH_3, 4·70% (0·91 mole), infra-red spectrum, 1760, 1722, 1595, 1511 cm^{-1} ($CHCl_3$).

The ether layer, which contained ketone XI, was dried with anhydrous sodium sulphate, chromatographed on alumina, and the second eluted fraction was collected. Removal of the solvent gave ketone XI, which was recrystallized from alcohol as yellow needles (10–20 mg), m.p. 103–105°, λ_{max} 248 mμ (log ε 4·20), 342 mμ (log ε 4·28), $[\alpha]_D^{21}$ +16·3°, (Found: C, 67·38; H, 6·49; N, 4·75. $C_{17}H_{19}O_4N$ requires: C, 67·76; H, 6·39; N, 4·65%), C—CH_3, 9·40% (1·88 moles).

Ozonolysis of aureothinic acid

A solution of 500 mg (1·74 mmoles) of X in 15 ml of chloroform was cooled to about −5° and ozone was passed through this solution till one equivalent amount (1·74 mmoles) of ozone was absorbed. The solution became almost colourless. The solvent was removed under reduced pressure at room temp and the resulting crystalline ozonide was decomposed in a flask fitted with a reflux condenser, by warming at 60° with 10 ml of water. The resultant oily material, insoluble in water, crystallized after cooling. The crystals were *p*-nitro-α-methylcinnamaldehyde as shown by infra-red measurement. The colorless aqueous layer obtained from the decomposition of the ozonide was distilled under reduced pressure into a 2,4-dinitrophenylhydrazine solution. From this solution, about 70 mg of hydrazone was obtained, which was chromatographed on alumina; this was identified as the 2,4-dinitrophenylhydrazone of formaldehyde, m.p. 156–158°, undepressed by admixture with an authentic sample. The unvolatile fraction remaining in the flask was a mixture of oily and crystalline materials and was acidic. The colour reaction for 1,2-dicarboxylic acids was positive. This acid (50 mg) was neutralized with sodium bicarbonate (50 mg) and treatment of this sodium salt with *p*-bromophenacyl bromide (280 mg) in ethanol–water yielded a crystalline substance which was recrystallized from acetone; this was the *p*-bromophenacyl ester of malic acid, m.p. 175–177°, confirmed by a mixed melting point test and comparison of infra-red spectrum with that of an authentic specimen.

Chromic acid oxidation of aureothinic ketone

By the Kuhn–Roth method, 10 mg of XI was oxidized and the product was distilled. To the distillate (50 ml) conc aqueous ammonia (5 ml) was added, and it was evaporated to dryness under diminished pressure. The residue was dissolved in a drop of water, and propionic acid and acetic acid were identified by a paper chromatographic method.

Alkaline degradation of aureothin

To a solution of I (2 g) in ethanol (16 ml) a solution of KOH (2 g) in water (7 ml) was added and the mixture was heated at 80° for 2 hr under nitrogen. Volatile carbonyl compounds were trapped by 2,4-dinitrophenylhydrazine solution and thus 10 mg of 2,4-dinitrophenylhydrazone was collected. The filtrate of the reaction mixture was neutralized with HCl, when a fairly large amount of precipitate appeared. After the filtration, a solution of 2,4-dinitrophenylhydrazine was added to this filtrate to give 10 mg of 2,4-dinitrophenylhydrazone. Recrystallization from alcohol gave crystals of m.p. 148–150°, undepressed on admixture with an authentic sample of 2,4-dinitrophenylhydrazone of diethyl ketone.

Alkaline degradation of isoaureothin

By the same method as described above, diethyl ketone was obtained from isoaureothin as 2,4-dinitrophenylhydrazone.

Alkaline degradation of desmethylisoaureothin

The starting material was recovered, even when somewhat drastic conditions were employed as compared with those in the case of aureothin.

Aureonone (XII)

A solution of I (3 g) in 30 ml of chloroform was cooled to about $-5° \sim -10°$ and ozone was passed through this solution till one equivalent amount of ozone was absorbed. The solvent was removed under reduced pressure at room temp and the resulting crystalline ozonide was decomposed in a flask fitted with reflux condenser, by warming at 60° with 10 ml of water for 1 hr. After cooling, the separated solid was treated with 10–15 ml of water at 80° five times. The water insoluble residue was mainly *p*-nitro-α-methylcinnamaldehyde. The combined solution of the filtrate and washings was distilled under reduced pressure into a solution of 2,4-dinitrophenylhydrazine to give 57 mg of yellow precipitate which was identified as 2,4-dinitrophenylhydrazone of formaldehyde by recrystallization. The unvolatile fraction remaining in the flask was an oily material (but partly crystalline), to which was added a small amount of methanol and on keeping in an ice box gave aureonone (XII) as prisms. The crystals were filtered and washed with ether–methanol. Removal of the solvent from the filtrate gave additional crystals, overall yield 180 mg. Recrystallization from a small amount of methanol gave crystals, m.p. 153–155°, λ_{max} 263 mμ (log ε 3·90), 248 mμ (log ε 3·84), (Found: C, 60·28; H, 6·01. $C_{12}H_{14}O_5$ requires: C, 60·50; H, 5·92%).

Isomerization of aureonone

On heating at 40° in ethanol containing a small amount of HCl, aureonone was easily isomerized. This was identified by the changes in its ultra-violet spectrum.

Isoaureonone (XIII)

A solution of 0·5 g of isoaureothin (III) in 15 ml of chloroform was cooled to $-5° \sim -10°$ and ozone was passed through this solution till 1·1 equivalent amount of ozone was absorbed. By the same method as described above, the ozonide of isoaureothin was obtained and then decomposed at 50° with 10 ml of water. After cooling, the separated solid was treated with 10 ml of hot water five times. The water insoluble residue was crystallized easily and was proved to be *p*-nitro-α-methylcinnamaldehyde. A combined solution of filtrate and washings was distilled under reduced pressure into a solution of 2,4-dinitrophenylhydrazine, to give 15 mg of yellow precipitate. The unvolatile residue was pale yellow oil. In spite of repeated purification by various methods, crystallization of this unvolatile substance (isoaureonone) did not take place, λ_{max} 294 mμ.

Methylation of desmethylisoaureothin with diazomethane

To a suspension of 870 mg of II in 30 ml of dry ether 50 ml of ethereal diazomethane solution, prepared from 1 g of nitrosomethylurea, was added dropwise over a period of 18 hr with vigorous stirring. During this period, the temp of the reaction mixture was maintained at 10–15° and traces of atmospheric moisture were excluded. After the diazomethane solution had been added, stirring was continued for 2 hr. The yellow crystalline solid was then filtered and washed with three 10 ml portions of ether. The ether washings were combined with the filtrate. The solid which separated was recrystallized from ethanol and 620 mg of isoaureothin (III) was obtained, m.p. 146–147°, undepressed on admixture with an authentic sample. Since aureothin does not form a hydrochloride in spite of the presence of the γ-pyrone structure, two isomeric methyl ethers, I and III, were separated by fractional crystallization from ethanol. Thus, the above ether filtrate and washings were combined and were evaporated to dryness *in vacuo*. Recrystallization of the resulting solid from ethanol gave a mixture of yellow prisms and of a small amount of light yellow needles. Two additional recrystallizations from ethanol gave 10 mg of aureothin (I), yellow prisms, m.p. 152–153°, undepressed on admixture with an authentic sample.

Methylation of desmethylisoaureothin with diemthyl sulphate

(a) II (1 g) was dissolved in 30 ml of hot 2 N NaOH solution. A clear brown solution was obtained. The crystals which separated on cooling were collected, washed with a small amount of cold alcohol

and dried. Light yellow needles, 1·1 g. The salt had no distinct melting point and decomposed at about 207–210° without melting.

(b) Methylation of the sodium salt of II: the sodium salt (1·1 g) was suspended in 40 ml of anhydrous acetone. Dimethyl sulphate (0·7 g) was added to the suspension and the mixture was refluxed for 6 hr, and allowed to stand overnight. The mixture was again warmed on a water bath for 5 min and was filtered. Recrystallization from alcohol twice gave yellow needles, m.p. 146°, undepressed on admixture with an authentic sample of III. yield, 200 mg. Spontaneous evaporation of each mother liquor from recrystallization gave 60 mg of brownish yellow prisms, m.p. 151–152°, which was found to be identical (by mixed m.p. and infra-red spectrum) with I.

The above acetone filtrate was diluted with 30 ml of water. The separated brown oil crystallized after 2 days. Recrystallization from alcohol gave an additional 180 mg of III. The mother liquor was evaporated as above, and 205 mg of I, m.p. 150–151° was obtained as brownish yellow prisms, total yield 62% (I, 265 mg; III, 380 mg). When the reaction mixture was refluxed for 5 hr, 40 mg of I and 110 mg of III was obtained from 230 mg of II (total yield, 63%). In another run, the reaction mixture was refluxed with 2 g of anhydrous K_2CO_3. From 1 g of the sodium salt, 150 mg of I and 250 mg of III were obtained (total yield, 41%). In each case, none of the starting material of II was recovered.

Aza-desmethylisoaureothin (XIV)

A suspension of 1 g of aureothin (I) in 10 ml of acetic acid containing 3 g of ammonium acetate was gently refluxed for 4 hr. To the cooled solution, 200 ml of water was added, when a brown oily layer at once separated and solidified. The liquid layer was removed by decantation, and the residue crystallized on the addition of 50 ml of hot ethanol. After washing three times with hot ethanol, the product was recrystallized from dimethylformamide; weight 250 mg, m.p. 238–239°, λ_{max} 341 mμ (log ε 4·25), 296 mμ (log ε 4·16), 245 mμ (log ε 4·18), (Found: C, 65·76; H, 5·95; N, 7·63. $C_{21}H_{22}O_3N_2$ requires: C, 65·95; H, 5·80; N, 7·33%).

In a solution of 1 ml of pyridine and 5 ml of acetic anhydride 20 mg of XIV was suspended. The mixture became a clear solution when kept at 70–80° for 30 min. Yellow precipitates were obtained from the cooled solution, by the addition of 20 ml of water. They were recrystallized from ethanol whereupon yellow needles of *aza-desmethylisoaureothin acetate* with m.p. 211–213° were obtained (15 mg), λ_{max} 325 mμ (log ε 4·32), 238 mμ (log ε 4·30).

Aza-desmethylisoaureonone acetate (XV)

A solution of 350 mg of aza-desmethylisoaureothin acetate in 15 ml of chloroform was cooled to $-5° \sim -10°$ and ozone was passed through this solution, until about one equivalent amount of ozone was absorbed. On removal of the solvent under reduced pressure, a gummy residue was obtained which was treated with 10 ml of water in a flask fitted with a reflux condenser at 60°. The aqueous layer in the flask was separated from the solid residue by decantation and the aqueous fraction was distilled under reduced pressure to give a slightly yellow residue, which on recrystallization from methanol, weighed 10 mg, m.p. 208–209°. No volatile carbonyl compound could be detected by distilling the aqueous fraction into a 2,4-dinitrophenylhydrazine solution. The solid residue, obtained from the decomposition of ozonide, consisted of two components; one was easily soluble in methanol, whereas the other was sparingly soluble. The former was identified as *p*-nitro-α-methylcinnamaldehyde by its melting point and infra-red spectrum. The latter, sparingly soluble in methanol, was recrystallized from methanol and gave 70 mg of colourless needles, which turned out to be identical with the crystals obtained from the water soluble fraction, as described above. The total amount was 80 mg, m.p. 209–210°, λ_{max} 304 mμ (log ε 3·85), 233 mμ (log ε 3·81), (Found: C, 58·86; H, 5·98; N, 5·45. $C_{13}H_{15}O_3N$ requires: C, 58·83; H, 5·70; N, 5·28%).

Aminol H (XVI)

When a solution of isoaureothamine (VII) (2 g) and $LiBH_4$ (180 mg) in purified tetrahydrofuran (60 ml) was warmed on a water bath, a reaction started with the generation of gas; about 30 min later, it was refluxed for 20 min, the excess $LiBH_4$ and complex were decomposed with water, and the solvent was removed under reduced pressure. To this residue, on adding water, an almost transparent solution was obtained: the aqueous layer (pH ca. 10) was neutralized to pH 5·5, the

precipitated crystals were collected, and the remaining product was extracted thrice with ether from the mother liquid. The combined reduction product was recrystallized from ethanol, the first crop being 1·2 g; an analytical sample was recrystallized from alcohol repeatedly, m.p. 156–158°, $[\alpha]_D^{27}$ +13° (CH_3OH), λ_{max} 304 mμ (log ε 4·47), (Found: C, 71·62; H, 7·58; N, 3·60. $C_{22}H_{27}O_4N$ requires: C, 71·52; H, 7·37; N, 3·79%), C—CH_3 10·25% (2·52 moles), OCH_3 8·08% (0·96 moles).

Aminol H was treated with diazomethane in ether when it methylated rather easily with the generation of gas. An oily product crystallized out during the course of several days. It was recrystallized from absolute ethanol by addition of petroleum ether, m.p. 92–94°, (*O-methyl aminol* H), (Found: C, 72·07; H, 7·39; N, 3·86. $C_{23}H_{29}O_4N$ requires: C, 72·03; H, 7·62; N, 3·65%), OCH_3, 14·93% (1·85 moles).

Aminol H was warmed in acetic anhydride for a few minutes and after decomposition of the acetic anhydride by pouring into water, an oily product was obtained; it was recrystallized from alcohol–petroleum ether repeatedly, m.p. 129–132°. It was shown to be *N-acetyl aminol H* from analytical and infra-red evidence.

Aminol H was dissolved in a small amount of acetic anhydride–pyridine mixture and the solution was warmed for a few minutes on a water bath. After cooling, the solution was diluted with ether and further petroleum ether was added until the solution became turbid. The solution was allowed to stand in an ice box when crystals appeared. Recrystallization from absolute ethanol–petroleum ether gave fine crystals of N,O-*diacetyl aminol* H, m.p. 94–95°, infra-red spectrum 1795, 1712, 1660, 1511 cm^{-1} (KBr). Treatment of this diacetyl derivative with water, gave N-acetyl aminol H.

N-*Acetyl* O-*methyl aminol* H was obtained in two ways: acetylation of O-methyl aminol H under the usual conditions (acetic anhydride–pyridine) or methylation of N-acetyl aminol H with diazomethane. Recrystallization from ethanol gave needles, m.p. 130–132°, λ_{max} 298 mμ (log ε 4·51), (Found: C, 70·56; H, 7·53; N, 3·43. $C_{23}H_{29}O_4N$ requires: C, 70·56; H, 7·34; N, 3·29%).

N-*Acetyl aminol* A (XVII)

To N-acetyl O-methyl aminol H (190 mg) in tetrahydrofuran (8 ml) lithium aluminium hydride (100 mg) in tetrahydrofuran was added and the mixture was stirred at room temp for 20 min. After addition of ethyl acetate to decompose the excess $LiAlH_4$, water saturated with Na_2SO_4 was added and then the solution was acidified with dilute HCl. The solution was extracted with ether. The ether extract was washed with $NaHCO_3$ solution, dried with Na_2SO_4 and concentrated under reduced pressure to give a yellow solid. Recrystallization from ethanol gave colourless needles of XVII, m.p. 155–156°, $[\alpha]_D^{27}$ +57·6° ($CHCl_3$), λ_{max} 300 mμ (log ε 4·54), (Found: C, 75·32; H, 8·02; N, 3·89. $C_{23}H_{29}O_3N$ requires: C, 75·17; H, 7·95; N, 3·81%).

Treatment of XVII with acetic anhydride–pyridine gave crystals of N,O-*diacetyl aminol* A, m.p. 144–146° (recrystallization from ethanol).

Lactol (XVIII)

To a mixture of 110 ml of ethanol and 55 ml of 3 N aq NaOH, 2 g of N-acetyl isoaureothamine was added. The flask was equipped with a reflux condenser and the suspension was warmed on a water bath at about 80° for 10 min, when the mixture became clear and of an orange colour. After rapid cooling, the solution was neutralized with dilute HCl; the solution turned yellow immediately at the neutralization point (pH 7). The solution was concentrated to 50 ml under reduced pressure to yield fine crystals (main portion was XVIII). After filtration, the yellow filtrate was acidified with dilute HCl and the resultant precipitates were collected and recrystallized from ethanol to yield colourless needles of XVIII, m.p. 170–171° (500 mg), $[\alpha]_D^{27}$ 0° ± 1·5° (CH_3OH), λ_{max} 299 mμ (log ε 4·52), (Found: C, 67·06; H, 7·19; N, 3·63. $C_{24}H_{29}O_6N$ requires: C, 67·43; H, 6·84; N, 3·28%). Measurement of the acidity constant (pKa) by the titration method was undertaken, but no consumption of alkali by the sample was observed below pH 10·5.

Action of acetic anhydride on lactol (XVIII)

To a mixture of 1 ml of pyridine and 5 ml of acetic anhydride 50 mg of XVIII was added. It was kept at 70° for ten min and after cooling, water was added to the solution, the resultant crystals were collected, recrystallized from ethanol and identified as the starting material, XVIII. The same procedure was applied with prolonged heating (1 hr); the resultant crystals, differing from XVIII,

were recrystallized from ethanol and were identified as N-acetyl isoaureothamine by the comparison of the infra-red spectra, m.p. 193–194°, $[\alpha]_D^{28}$ 0° ± 2° ($CHCl_3$—CH_3OH (1:2)), [cf. N-acetyl isoaureothamine prepared from aureothin, m.p. 214–215°, $[\alpha]_D^{28}$ +140° ± 1·5° ($CHCl_3$—CH_3OH (1:2)]. On mixing two species of N-acetyl isoaureothamine (optical active and inactive species), no depression of m.p. was observed; mixed melting point, 193–200°, (Found: C, 70·59; H, 6·50. $C_{28}H_{37}O_5N$ requires: C, 70·40; H, 6·50%).

Racemic N-acetyl isoaureothamine was also obtained by treatment of XVIII with diazomethane.

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THE STRUCTURE OF PSORALIDIN

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Abstract—Psoralidin, $C_{20}H_{16}O_5$ the phenolic coumarin of *Psoralea corylifolia* Linn. has been shown to possess two hydroxyl groups, one conjugated δ-lactone, one isopentenyl group and an intramolecular ether linkage. On systematic degradation dihydropsoralidin dimethyl ether gave 2-hydroxy-4-methoxybenzaldehyde and 2,4-dimethoxy-5(-3-methylbutyl)-benzoic acid. The synthesis of the latter compound has been described. On the basis of the degradation experiments coupled with ultra-violet and infra-red absorption data, the structure of psoralidin has been established as 6-(3-methylbut-2-enyl)-coumestrol (IV, R = H).

PREVIOUSLY we have identified[1a] the sterol of the seeds of *Psoralea corylifolia* Linn. as stigmasterol and have shown[1b] that the furocoumarins psoralen and isopsoralen can be isolated from the glycosidic fraction of the seed kernel. The present communication deals with the structure elucidation of the phenolic coumarin, psoralidin, first isolated from the pericarp of the seeds of *P. corylifolia* by Chakravarti *et al.*[2] and assigned the molecular formula $C_{16}H_{14}O_4$. This group of workers suggested the presence of a phenolic hydroxyl group, a lactone group and an isopentenyl group in the molecule of psoralidin. Acetone was isolated from the chromic acid oxidation of psoralidin. On the basis of these findings, these workers suggested[2] the provisional structure IA for the coumarin.

By following the scheme for isolation outlined by Chakravarti *et al.*[2] we failed to isolate psoralidin from the pericarp of the seeds. Nevertheless, we have been able to isolate from the phenolic fraction of the alcoholic extract of the seed kernel, a crystalline compound, m.p. 290–292°d in 0·16 per cent yield, which was identified[3] as psoralidin by direct comparison of its methyl ether, m.p. 190–191° with psoralidin methyl ether, m.p. 190° of Chakravarti *et al.*[4] (mixed m.p., infra-red and paper chromatography[5]).

Since the ultra-violet absorption spectra of the acetate of a phenolic coumarin is identical with that of the corresponding desoxycoumarin,[6] we first tried to compare the ultra-violet absorption spectra of psoralidin acetate with that of psoralen IB. The vast difference between the spectra of the two compounds makes the structure IA of Chakravarti *et al.* for psoralidin untenable. So we thought it desirable to make a systematic investigation on the structure of psoralidin. We observed[3] that psoralidin has the molecular formula $C_{20}H_{16}O_5$ and not $C_{16}H_{14}O_4$ as suggested by Chakravarti *et al.*, from the consideration of the analytical data and molecular weight of its methyl ether. The presence of two phenolic hydroxyl groups is indicated by the analysis of the methyl ether, which shows the presence of two methoxy groups, whereas psoralidin

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shows the presence of none. Further psoralidin forms a diacetate,[3] $C_{24}H_{20}O_7$, m.p. 221–223° (reported,[2] m.p. 220°).

The infra-red spectra of psoralidin in KBr disk show peaks at 3350 (phenolic hydroxyl), 1710 (conjugated δ-lactone), 1625 (conjugated C=C), 1600, 1578 and 1498 (aromatic nucleus) and 1261 cm^{-1} (aromatic C—O[7,8]).

Psoralidin dimethyl ether does not show any hydroxyl peak in the infra-red spectra but shows peaks at 1732 (conjugated δ-lactone), 1638 (conjugated C=C), 1604, 1570 and 1500 (aromatic nucleus) and 1261 cm^{-1} (aromatic C—O). Psoralidin diacetate shows infra-red peaks at 1740 (acetate and lactone), 1625 (conjugated C=C), 1600, 1575 and 1498 (aromatic nucleus) and 1225 cm^{-1} (acetate). Thus of the five oxygen atoms of psoralidin, two are present in two phenolic hydroxyl groups and two in a conjugated δ-lactone group. The fifth oxygen atom is present as an ether,[3] as shown by the peaks at 1261 and 1094 cm^{-1} in the infra-red spectra of psoralidin.

The ultra-violet absorption spectra of psoralidin show peaks at 208, 244, 305 and 347 mμ (Table 1). Psoralidin dimethyl ether shows similar spectra, whereas psoralidin

TABLE 1. ULTRA-VIOLET ABSORPTION DATA*

Psoralidin	λ_{max}	208 (40,800), 244 (20,300), 305 (7000) and 347 mμ (25,300)
Psoralidin dimethyl ether	λ_{max}	208 (42,600), 243 (24,000), 304 (8500) and 344 mμ (28,500)
Wedelolactone[12]	λ_{max}	211 (37,400), 250 (19,200), 303 (8200) and 350 mμ (22,700)
Wedelolactone trimethyl ether[13]	λ_{max}	247 (18,620), 300 (6300) and 350 mμ (22,400)
Coumestrol[12]	λ_{max}	244 (—), 304 (—) and 343 mμ (—)

* ε values are given in parentheses

diacetate shows maxima at 207, 225 300 and 330 mμ. The ultra-violet absorption spectra of psoralidin and its dimethyl ether are so strikingly similar to those of wedelolactone (II)[9,10] and coumestrol (III)[11,12] that we were led to believe that psoralidin has the same skeletal structure as that of these two compounds. Finally we have been able to establish[3b] that psoralidin is in fact 6-(3-methylbut-2-enyl)-coumestrol (IV, R = H) following the series of reactions described below.

Psoralidin (IV, R = H) and its dimethyl ether (IV, R = Me) smoothyl absorbed one mole of hydrogen in presence of palladium on charcoal catalyst to yield dihydropsoralidin (V, R = H), m.p. 274–276° and dihydropsoralidin dimethyl ether (V, R = Me), m.p. 193–195° respectively. The ultra-violet absorption spectra of the dihydro-compounds are similar to those of psoralidin and its dimethyl ether, thus establishing the presence of a non-conjugated ethylenic linkage in the molecule of

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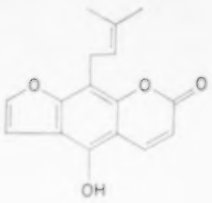
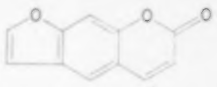


I A



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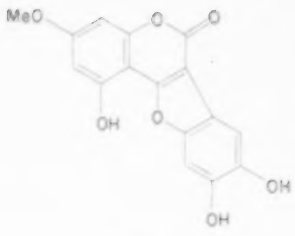

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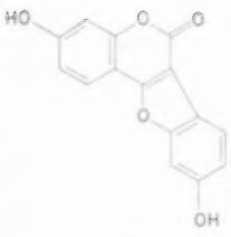
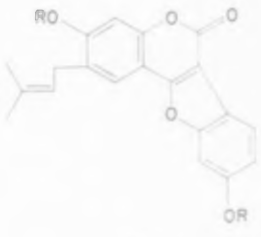
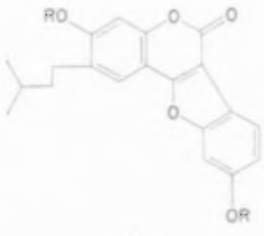


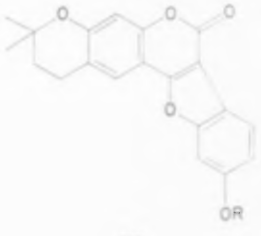
III



IV



V



VI

psoralidin. On repeating the chromic acid oxidation experiment[2] on psoralidin dimethyl ether, we also have been able to isolate acetone (identified as its 2,4-dinitrophenyl hydrazone). This experiment establishes the presence of the group $(CH_3)_2{\cdot}C{=}C$ in psoralidin. Further, dihydropsoralidin on treatment with fuming nitric acid gives isocaproic acid, identified be paper chromatography.[5] This experiment confirms the presence of the group $(CH_3)_2{\cdot}C{=}CH{\cdot}CH_2{-}$ directly attached to the aromatic nucleus,

as originally suggested by Chakravarti *et al.*[2] On treatment with methanolic hydrochloric acid, psoralidin undergoes isomerization to the monohydroxy chroman (VI, R = H), m.p. 284–287°, having identical ultra-violet asborption spectra with those of psoralidin. The chroman (VI, R = H) forms a monomethyl ether (VI, R = Me), m.p. 172–174° and 197–200°. The formation of the chroman (VI, R = H), which we name isopsoralidin establishes[14] that the isopentenyl group must be situated at the *ortho*-position to one of the two phenolic hydroxyl groups in psoralidin.

On fusion with potassium hydroxide, psoralidin gives,[3] as expected, resorcinol and β-resorcylic acid (identified as its methyl ester). The presence of a coumarin type structure is demostrated by the fact that on treating psoralidin dimethyl ether (IV, R = Me) alternately with methanolic alkali and dimethyl sulphate, methyl psoralidinate trimethyl ether (VII), m.p. 114–115° is isolated. The infra-red spectra of this ester show a peak at 1705 cm^{-1} (conjugated ester) and the ultra-violet absorption spectra show maxima at 206, 229 and 325 mμ.

Similar treatment of dihydropsoralidin dimethyl ether (V, R = Me) with alkali and dimethyl sulphate yields methyl dihydropsoralidinate trimethyl ether (VIII, R = Me) as an oil, which on saponification affords[3] dihydropsoralidinic acid trimethyl ether (VIII, R = H), m.p. 197–198°d, having ultra-violet absorption maxima at 212 and 319 mμ. The latter compound on sublimation in vacuum smoothly eliminates a molecule of carbon dioxide and forms the decarboxy-compound (IX), m.p. 84–86°, which does not show any carbonyl peak in the infra-red spectra, but shows peaks at 1620 (C=C), 1582 and 1496 (aromatic nucleus), 1264 (aromatic C—O), 1110 (aromatic ether) and 1035 cm^{-1} (OMe).[5]

The decarboxy derivative (IX) on treatment with osmium tetroxide is expected to give the diol (X). But instead of the diol, we have been able to isolate only a light yellow crystalline compound, $C_{22}H_{28}O_6$, m.p. 113–115° to which we assign the benzoin structure (XI) on the following grounds. The compound is soluble in alkali and gives blue-violet colouration with alcoholic ferric chloride. The ultra-violet absorption spectra show maxima at 212, 230, 279 and 326 mμ and the infra-red spectra show peaks at 3500 (hydroxyl), 1635 (conjugated carbonyl) and 1605, 1575 and 1498 cm^{-1} (aromatic nucleus). It may be presumed that the benzoin (XI) has been formed through the intermediate hemiketal (X), which we have failed to isolate.

The benzoin (XI) was next oxidized with sodium periodate to yield 2-hydroxy-4-methoxybenzaldehyde (identified by paper chromatography of its 2,4-dinitrophenyl hydrazone[5]) and an acid, m.p. 90–91°, which was found to be identical (mixed m.p. and infra-red) with 2,4-dimethoxy-5-(3-methylbutyl)-benzoic acid (XII), synthesized by us by an unambiguous method described below.

Friedel-Craft's reaction between methyl β-resorcylate and isovaleryl chloride afforded methyl 2,4-dihydroxy-5-isovaleryl benzoate (XIII, R = H), m.p. 72–74° which was previously prepared[15] by the hydrogenation of methyl 2,4-dihydroxy-5-($\beta\beta$-dimethyl acrylyl)-benzoate. The dimethyl ether (XIII, R = Me), m.p. 129–130° of the phenolic keto-ester (XIII, R = H) on catalytic hydrogenation[16] in presence of perchloric acid gave an oily ester, which was directly saponified to give the acid (XII) m.p. 90–91°.

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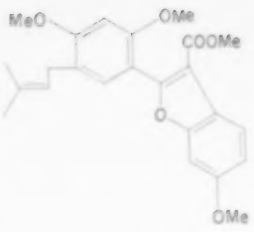

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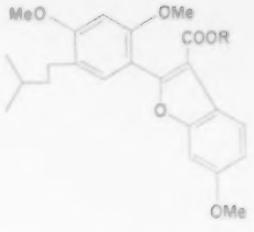

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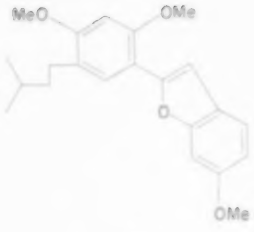

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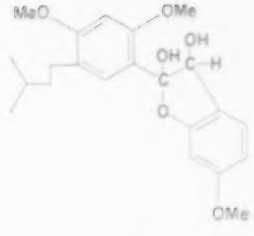

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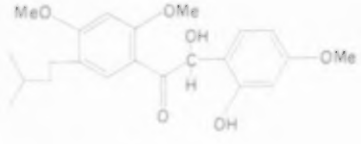

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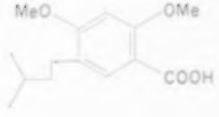

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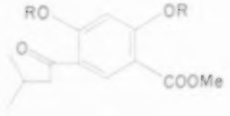
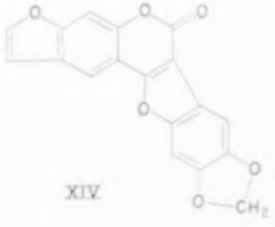


XIII



XIV

Thus psoralidin (IV, R = H) is a new addition to the family of benzfuranocoumarins of which wedelolactone (II), coumestrol (III) and erosnin (XIV)[8] were the pre-previously known members.

EXPERIMENTAL

The ultra-violet absorption spectra were measured in 95% ethyl alcohol and the infra-red spectra were measured in chloroform unless otherwise stated.

Isolation of psoralidin (IV, R = H)

1·5 Kg of defatted and powdered seed-kernel[15] of *P. corylifolia* was extracted for 20 hr with 95% ethyl alcohol in a Soxhlet. The residue, obtained after the removal of ethanol was taken up in ether and extracted with cold 5% aqueous NaOH. The alkaline layer was acidified with cold dil HCl and

the precipitated material reextracted with ether, washed with water and dried (Na_2SO_4). On careful concentration, crude psoralidin (2·47 g, 0·16% yield on seed-kernel), m.p. 283–288° d was obtained. Repeated crystallization from acetone afforded the analytical sample of psoralidin (IV, R = H), m.p. 290–292° d R_f 0·78[17] (Reported[2] m.p. 315° d). It shows violet fluorescence in dil ethanolic solution (Found: C, 71·12; H, 4·93. $C_{20}H_{16}O_5$ requires: C, 71·42; H, 4·80%).

U.V. (a) See Table 1.

(b) In 0·1 N KOH in EtOH. . . λ_{max} 256 (ε 14,700), 285 (ε 18,500) and 395 mμ (ε 26,900).

I.R. (KBr) Peaks at 3350 (hydroxyl), 1710 (conjugated δ-lactone), 1625 (conjugated C=C), 1600, 1578 and 1498 (aromatic nucleus) and 1261 and 1094 cm^{-1} (aromatic C—O).

Psoralidin dimethyl ether (IV, R = Me)

A mixture of psoralidin (0·5 g), anhydrous potassium carbonate (4 g), dimethyl sulphate (4 cc) and acetone (60 cc) was refluxed for 5 hr. The crude solid isolated in the usual manner on crystallization from acetone gave psoralidin dimethyl ether (IV, R = Me; 0·4 g), m.p. 190–191°, R_f 0·63,[17] identical with the psoralidin methyl ether of Chakravarti *et al.* (mixed m.p., infra-red and paper chromatography). It shows violet fluorescence in dil ethanolic solution. (Found: C, 72·34; H, 5·68; OMe, 17·67. $C_{22}H_{20}O_5$ requires: C, 72·51; H, 5·53; OMe (two), 17·04%).

Mol. Wt. Found (Rast), 352. Calc., 364.

U.V. (a) See Table 1.

(b) In 0·1 N KOH in EtOH. . . λ_{max} 224 (ε 27,800), 304 (ε 7200) and 345 mμ (ε 11,200).

I.R. Peaks at 1732 (conjugated δ-lactone), 1638 (conjugated C=C), 1604, 1570 and 1500 (aromatic nucleus) and 1261 cm^{-1} (aromatic C—O).

Psoralidin diacetate (IV, R = Ac)

Psoralidin (75 mg) was acetylated in the usual manner with acetic anhydride (2 cc) and pyridine (2 cc). The crude solid on crystallization from ethyl acetate afforded psoralidin diacetate (IV, R = Ac), m.p. 221–223°. (Reported[2] m.p. 220°). (Found: C, 68·06; H, 4·89. $C_{24}H_{20}O_7$ requires: C, 68·56; H, 4·80%).

U.V. λ_{max} 207 (ε 39,900), 225 (ε 30,100), 300 (ε 13,650) and 330 mμ (ε 24,000).

I.R. Peaks at 1740 (acetate and lactone), 1625 (conjugated C=C), 1600, 1575 and 1498 (aromatic nucleus) and 1225 cm^{-1} (acetate).

Isopsoralidin (VI, R = H)

A mixture of psoralidin (1 g), methanol (100 cc) and conc HCl (28 cc) was refluxed for 2 hr and allowed to stand overnight at room temp. The crystalline material that separated out gave on crystallization from methanol isopsoralidin (VI, R = H; 0·49 g), m.p. 284–287°. The mixed m.p. with psoralidin was depressed. It showed violet fluorescence in dil ethanolic solution. (Found: C, 71·78; H, 5·18. $C_{20}H_{16}O_5$ requires: C, 71·42; H, 4·80%).

U.V. λ_{max} 209 (ε 44,700), 246 (ε 22,400), 306 (ε 8200) and 349 mμ (ε 29,100).

Isopsoralidin monomethyl ether (VI, R = Me)

A mixture of isopsoralidin (0·31 g), acetone (30 cc), anhydrous potassium carbonate (2 g) and dimethyl sulphate (1·8 cc) was refluxed for 5 hr. The crude solid on crystallization from a mixture of acetone and methanol afforded isopsoralidin methyl ether (VI, R = Me; 0·18 g), m.p. 172–174° and 197–200°. (Found: C, 71·67; H, 5·17. OMe, 9·12. $C_{21}H_{18}O_5$ requires: C, 71·99; H, 5·18, OMe (one), 8·86%).

U.V. λ_{max} 211 (ε 42,100), 244 (ε 22,200), 306 (ε 9200) and 346 mμ (ε 30,800).

Dihydropsoralidin (V, R = H)

A mixture of psoralidin (1·2 g), ethyl acetate (400 cc) and 10% palladium on charcoal catalyst (0·5 g) was stirred in an atmosphere of hydrogen. One mole of hydrogen was absorbed in 15 min

[17] The paper chromatography was run[5] on Whatman No. 1 filter paper using ethanol : water (3 : 1) as the developing solvent. The spot was detected by the blue-violet fluorescence in ultra-violet light. D. P. Chakraborty and P. K. Bose, *J. Ind. Chem. Soc.* 33, 905 (1956).

and after that there was no appreciable uptake of hydrogen. The hydrogenated product on crystallization from ethyl acetate afforded dihydropsoralidin (V, R = H; 0·85 g), m.p. 274–276°. (Found: C, 71·39; H, 5·09. $C_{20}H_{18}O_5$ requires: C, 70·99; H, 5·36%)
U.V. λ_{max} 210 (ε 39,000), 244 (ε 22,000), 305 (ε 7500) and 345 mμ (ε 27,700).

Dihydropsoralidin dimethyl ether (V, R = Me)

(a) A mixture of psoralidin dimethyl ether (0·8 g), ethyl acetate (300 cc) and 10% palladium on charcoal catalyst (0·2 g) was stirred in an atmosphere of hydrogen. One mole of hydrogen was absorbed in 20 min. The hydrogenated product on crystallization from acetone afforded dihydropsoralidin dimethyl ether (V, R = Me; 0·65 g), m.p. 193–195°. (Found: C, 71·62; H, 6·16. $C_{22}H_{22}O_5$ requires: C, 72·11; H, 6·05%).
U.V. λ_{max} 209 (ε 39,100), 243 (ε, 21,600), 304 (ε 7700) and 344 mμ (ε 26,500).

(b) A mixture of dihydropsoralidin (0·25 g), anhydrous potassium carbonate (2 g), dimethyl sulphate (1·75 cc) and acetone (30 cc) was refluxed for 5 hr. Dihydropsoralidin dimethyl ether (0·2 g) thus obtained melted at 192–195° and was identical with the material reported above.

Alkali fusion of psoralidin

Isolation of resorcinol and β-resorcylic acid. An intimate mixture of psoralidin (1 g) and potassium hydroxide (5 g) was heated to 300° (bath). The temp was then lowered to 250° (bath) and kept at that temp for 1 hr. The fused mass was dissolved in water, acidified and extracted with ether. The ether solution was washed with Na_2CO_3 solution, then with water, dried (Na_2SO_4) and evaporated to furnish a brown gummy residue (0·4 g), which on evaporative distillation at 130–140°/2 mm gave resorcinol, m.p. 100–104° identical with an authentic specimen (mixed m.p. and infra-red). (Found: C, 65·36; H, 5·29. Calc. for $C_6H_6O_2$: C, 65·44; H, 5·49%).

From the carbonate soluble fraction was obtained, on acidification and extraction with ether, a gummy acid (0·29 g), which on esterification with ethereal diazomethane followed by sublimation at 110–115°/0·3 mm yielded methyl β-resorcylate, m.p. 115–117°, identical (mixed m.p. and infra-red) with an authentic specimen. (Found: C, 57·23; H, 4·77. Calc. for $C_8H_8O_4$: C, 57·14; H, 4·80%).

Chromium trioxide oxidation of psoralidin dimethyl ether

Isolation of acetone. A mixture of psoralidin dimethyl ether (0·36 g), chromium trioxide (0·85 g), glacial acetic acid (15 cc) and water (5 cc) was allowed to stand at room temp for 70 hr. The reaction mixture was diluted with water and steam distilled. To the distillate 2,4-dinitrophenyl hydrazine reagent[18] was added when an immediate precipitate was obtained. The precipitate on crystallization from methanol yielded 2,4-dinitrophenyl hydrazone of acetone, m.p. 126°, identical with an authentic specimen (mixed m.p.). (Found: C, 45·14; H, 4·40. Calc. for $C_9H_{10}O_4N_4$: C, 45·38; H, 4·23%).

Nitric acid oxidation of dihydropsoralidin

Isolation of isocaproic acid. Nitric acid (*d* 1·42, 11·7 cc) was cautiously added with cooling to dihydropsoralidin (0·87 g) and the mixture was kept at room temp for 66 hr, then diluted with water (330 cc) and again kept for 48 hr. Finally the reaction mixture was further diluted with water (780 cc) and steam-distilled. The first 500 cc of the distillate was cooled, saturated with NaCl and extracted with ether. The ether solution on evaporation gave an oil (56 mg) with characteristic odour of isocaproic acid. The presence of isocaproic acid in the oil was established by paper chromatography.[5,19] The solvent system[20] used was ethanol (95%): ammonia (sp. gr. 0·99): water (80 : 5 : 15). Whatman No. 1 filter paper was used. The chromatogram was sprayed with bromocresol green (pH 7), when yellow spot (R_f 0·58) was detected. This was identified as isocaproic acid by co-chromatogram with a pure specimen of isocaproic acid.

Methyl psoralidinate trimethyl ether (VII)

Psoralidin dimethyl ether (100 mg) was dissolved in 10% methanolic KOH solution (20 cc) by heating. The warm solution was alternately treated several times with dimethyl sulphate and aqueous

[18] A. L. Wilds in *Organic Reactions* (Edited by Roger Adams) Vol. II, p. 200. John Wiley, New York (1944).
[19] D. P. Burma and B. Banerjee, *J. Ind. Chem. Soc.* **28**, 135 (1951).
[20] A. G. Long, J. R. Quayle and R. J. Stedman, *J. Chem. Soc.* 2197 (1951).

10% KOH solution, in such a way that the final reaction mixture remained slightly alkaline. Extraction with ether in the usual manner gave a crude solid (60 mg), m.p. 102–105°, which on crystallization from methanol furnished the ester (VII), m.p. 114–115°. It showed bluish-violet fluorescence in dil ethanol. (Found: C, 70·24; H, 6·28. $C_{24}H_{26}O_6$ requires: C, 70·23; H, 6·39%).
U.V. λ_{max} 206 (ε 40,300), 229 (ε 30,400) and 325 mμ (ε 16,500).
I.R. Peaks at 1705 (conjugated ester), 1620 (conjugated C—C) and 1598 and 1500 cm^{-1} (aromatic nucleus).

Dihydropsoralidinic acid trimethyl ether (VIII, R = H)

Similarly dihydropsoralidin dimethyl ether (0·9 g) in 10% methanolic KOH solution (125 cc) on alternate treatment with dimethyl sulphate and 10% aqueous KOH solution yielded the dihydroester (VIII, R = Me; 0·58 g) as an oil, λ_{max} 207 (E 32,600), 227 (E 29,700) and 325 mμ (E 15,500), which resisted all attempts at crystallization.

The oil (0·5 g) was refluxed for 6 hr with 10% methanolic NaOH solution (5 cc), then cooled, diluted with water and acidified with cold dil HCl, when a crystalline solid was obtained. On crystallization from methanol the solid gave the acid (VIII, R = H; 0·42 g), m.p. 197–198° d. (Found: C, 68·99; H, 6·53. $C_{23}H_{26}O_6$ requires: C, 69·33; H, 6·58%).
U.V. λ_{max} 212 (ε 35,200) and 319 mμ (ε 20,000).
I.R. Peaks at 1678 (conjugated carboxyl), 1620 (conjugated C—C) and 1582 and 1498 cm^{-1} (aromatic nucleus).

2-(2,4-*Dimethoxy*-5-(3-*methylbutyl*)-*phenyl*)-6-*methoxy benzofuran* (IX)

An intimate mixture of dihydropsoralidinic acid trimethyl ether (1·2 g) and glass powder (0·2 g) was heated at 210° (bath) for 2 hr. The reaction mixture on sublimation at 190°/0·2 mm furnished the benzofuran (IX; 0·97 g), m.p. 80–83°. On crystallization from methanol, the analytical sample melted at 84–86°. (Found: C, 74·33; H, 7·02. $C_{22}H_{26}O_4$ requires: C, 74·55; H, 7·39%).
U.V. λ_{max} 212 (ε 34,000), 281 (ε 13,000), 223 (ε 37,300) and 338 mμ (ε 36,100).
I.R. Peaks at 1620 (conjugated C—C), 1582 and 1496 (aromatic nucleus), 1264 (aromatic C—O), 1110 (aromatic ether) and 1035 cm^{-1} (OMe).

Osmium tetroxide oxidation of the benzofuran (IX)

Isolation of the benzoin (XI). A solution of osmium tetroxide (0·69 g) in benzene (3·5 cc) was added to a solution of the benzofuran (IX, 1·03 g) in benzene (3 cc) and pyridine (8 drops) and the reaction mixture was allowed to stand at room temp for 5 days. The black osmate derivative was decomposed by stirring for 20 hr at room temp with ethanol (27 cc) and saturated aqueous Na_2SO_3 solution (27 cc). The mixture was then diluted with water (200 cc) and extracted with ether. The ether solution on evaporation furnished a gummy residue (0·89 g), which on crystallization from methanol gave the benzoin (XI, 0·38 g), m.p. 104–108°. On recrystallization from methanol, the analytical sample melted at 113–115°. It gave a blue-violet colour with alcoholic ferric chloride solution. (Found: C, 68·37; H, 6·96. $C_{22}H_{28}O_6$ requires: C, 68·02; H, 7·27%).
U.V. λ_{max} 212 (ε 35,400), 230 (ε 24,000), 279 (ε 21,300) and 326 mμ (ε 18,000).
I.R. Peaks at 3500 (hydroxyl), 1635 (conjugated ketone) and 1605, 1575 and 1498 cm^{-1} (aromatic nucleus).

Periodate oxidation of the benzoin (XI)

Isolation of 2-*hydroxy*-4-*methoxy-benzaldehyde and* 2,4-*dimethoxy*-5-(3-*methylbutyl*)-*benzoic acid* (XII). A solution of the benzoin (XI, 0·79 g), sodium metaperiodate (0·87 g), methanol (50 cc) and water (5 cc) was allowed to stand at room temp for 24 hr. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed with cold 5% aqueous Na_2CO_3, then with water, dried (Na_2SO_4) and evaporated to give trace of an oil, λ_{max} 230, 279 and 315 mμ, which was converted to its 2,4-dinitrophenyl hydrazone and was found to be identical with the 2,4-dinitrophenyl hydrazone of 2-hydroxy-4-methoxy-benzaldehyde (R_f 0·62) by paper chromatography.[21]

The above aqueous carbonate solution on acidification with dil HCl yielded a crystalline acid (60 mg), m.p. 80–84°, which on crystallization from cyclohexane gave the acid (XII), m.p. 90–91°,

[21] The developing solvent was ethanol : formamide : water (8 : 1 : 1).

identical (mixed m.p. and infra-red) with an authentic specimen described below. (Found: C, 66·37; H, 7·80. $C_{14}H_{20}O_4$ requires: C, 66·64; H, 7·99%).
I.R. Peaks at 1720 (conjugated carbonyl), 1610, 1580 and 1500 (aromatic nucleus), 1270 and 1110 (aromatic ether) and 1027 cm^{-1} (OMe).

2,4-Dinitrophenyl hydrazone of 2-hydroxy-4-methoxy-benzaldehyde (authentic)

2-Hydroxy-4-methoxy-benzaldehyde,[22] m.p. 40–41° was converted in the usual manner to its 2,4-dinitrophenyl hydrazone, which after crystallization from benzene melted at 264° (Reported[23] m.p. 256°). (Found: C, 50·58; H, 3·79. Calc. for $C_{14}H_{12}O_6N_4$: C, 50·60; H, 3·64%).

Synthesis of 2,4-dimethoxy-5-(3-methylbutyl)-benzoic acid (XII)

Methyl 2,4-dihydroxy-5-isovaleryl benzoate (XIII, R = H). To a cold solution of methyl β-resorcylate (3·8 g) in nitrobenzene (45 cc) was added powdered aluminium chloride (6·6 g) with stirring. The mixture was stirred until the entire aluminium chloride dissolved to form a light brown viscous mass. To this viscous solution was added freshly distilled isovaleryl chloride (3·1 g) in nitrobenzene (60 cc) and the solution stirred for 10 hr at 40–45°. Finally the reaction mixture was poured into ice and conc HCl and extracted with ether. The residue after the removal of ether gave crystals (4·6 g), m.p. 65–72° on cooling. The crystals on sublimation followed by crystallization from aqueous methanol gave the ester (XIII, R = H), m.p. 70–72° (Reported[15] m.p. 74°).
U.V. λ_{max} 244 (ε 45,800) and 313 mμ (ε 5900)

2,4-dinitrophenyl hydrazone of the above keto-ester was prepared in 85% yield in the usual manner. On crystallization from methanol it melted at 202–203° (Found: C, 52·50; H, 4·64. $C_{19}H_{20}O_8N_4$ requires: C, 52·78; H, 4·66%)

Methyl 2,4-dimethoxy-5-isovaleryl-benzoate (XIII, R = Me)

A mixture of the keto-ester (XIII, R = H, 0·6 g), anhydrous potassium carbonate (7 g), acetone (30 cc) and dimethyl sulphate (7 cc) was refluxed for 6 hr. On usual working up a crystalline solid (0·51 g), m.p. 120–125° was obtained. The solid, which showed negative ferric chloride test, on crystallization from methanol yielded the keto-ester (XIII, R = Me), m.p. 129–130°. (Found: C, 64·07; H, 7·28. $C_{15}H_{20}O_5$ requires: C, 64·27; H, 7·19%).
U.V. λ_{max} 239 (ε 29,600), 272 (ε 13,200) and 299 mμ (ε 5400).

2,4-Dimethoxy-5-(3-methylbutyl)-benzoic acid (XII)

A mixture of the keto-ester (XIII, R = Me, 0·36 g), glacial acetic acid (20 cc), 10% palladium on charcoal catalyst (0·1 g) and perchloric acid (0·1 cc) was stirred in an atmosphere of hydrogen. Two mole equivalent of hydrogen was absorbed in 15 min, then the hydrogenated product was worked up in the usual manner to yield a gum (0·35 g), which was saponified by refluxing for 2 hr with 5% methanolic KOH solution (5 cc). The reaction mixture on dilution followed by acidification yielded a crystalline acid (0·28 g), m.p. 84–85°, which on crystallization from cyclohexane furnished the acid (XII), m.p. 90–91°, identical (mixed m.p. and infra-red) with the acid (XII) obtained from psoralidin reported above. (Found: C, 66·59; H, 8·00. $C_{14}H_{20}O_4$ requires: C, 66·64; H, 7·99%).

Acknowledgements—We are highly indebted to Dr. George R. Petit of the University of Maine, Orono, Maine, U.S.A., to Dr. E. J. Eisenbraun, Stanford University, Stanford, California, U.S.A. and to Dr. Tapan K. Mukerji for the infra-red spectra of our compounds. We are also indebted to Dr. (Mrs.) A. Chatterjee, University College of Science, Calcutta, for the gift of osmium tetroxide and to Mr. P. Bagchi, Research Director, E. I. P. W. Ltd. for encouragement.

[22] H. A. Offe and H. Jatzkewitz, *Chem. Ber.* **80**, 469 (1947).
[23] F. Weygand and R. Mitgan, *Chem. Ber.* **88**, 301 (1955).

Tetrahedron, 1961, Vol. 14, pp. 284 to 287. Pergamon Press Ltd. Printed in Northern Ireland

CHEMICAL EXAMINATION OF *TYLOPHORA ASTHMATICA*—IV[1]

SYNTHESIS OF TYLOPHORINE[2]

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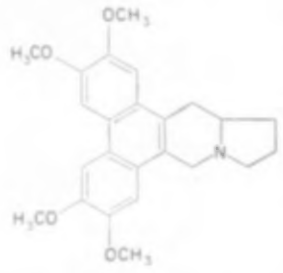
(*Received* 6 *March* 1961)

Abstract—Structure (I) assigned to tylophorine has been confirmed by a total synthesis.

TYLOPHORINE, the major alkaloid from *Tylophora asthmatica* Wight et Arn (Asclepiadaceae) has been shown to be 2,3,6,7-tetramethoxyphenanthro(9,10:6′,7′)indolizidine (I) on the basis of degradation studies.[1,3]



I

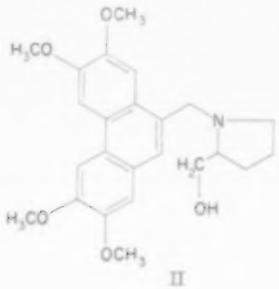
It was considered of interest to establish this structure by synthesis. The synthesis of the parent system, phenanthro(9,10:6′,7′)indolizidine, was reported in an earlier paper.[3] However, this method could not be applied to the synthesis of tylophorine itself, since the condensation of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde with δ-nitrobutyl benzoate yielded a complex mixture of as yet unidentified products, but not the desired nitropentene.

A second approach was based on the lines of Marchini and Belleau's synthesis[4] of cryptopleurine. Here again no basic product could be obtained from the condensation of 2,3,6,7-tetramethoxy-9-chloromethyl-phenanthrene with proline ester, self condensation of the latter apparently proceeding much faster than reaction with the halide. The halide condensed in good yield with prolinol to yield N-(2,3,6,7-tetramethoxy-phenanthrylmethyl)prolinol (II) which could not however be cyclized to tylophorine under a variety of conditions attempted.

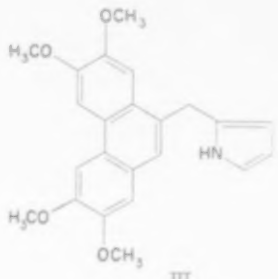
Finally, a successful synthesis of tylophorine was effected on the following lines: Treatment of pyrrylmagnesium bromide with 2,3,6,7-tetramethoxy-9-chloromethyl-phenanthrene yielded 2-(2,3,6,7-tetramethoxy-9-phenanthrylmethyl)pyrrole (III). This

[1] Part III, T. R. Govindachari, M. V. Lakshmikantham, B. R. Pai and S. Rajappa, *Tetrahedron* **9**, 53 (1960).
[2] A part of this work has been published in the form of a brief note: T. R. Govindachari, M. V. Lakshmikantham and S. Rajadurai, *Chem. & Ind.* 664 (1960).
[3] T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958).
[4] P. Marchini and B. Belleau, *Canad. J. Chem.* **36**, 581 (1958).

was reduced in acetic acid solution in the presence of Adams catalyst to the corresponding pyrrolidine (IV). The N-formyl derivative of this base (IVa) underwent smooth cyclization to the quaternary salt (V) on heating with phosphorus oxychloride in toluene. The last compound was reduced without further purification in good yield to (±)2,3,6,7-tetramethoxyphenanthro(9,10:6′,7′)indolizidine (I). After purification by chromatography and crystallization from chloroform–ethanol, the product melted at 289° (decomp) when introduced in a bath preheated to 250° as did (−)tylophorine and a mixture melted with decomposition at 282°.



II



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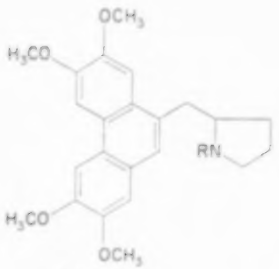
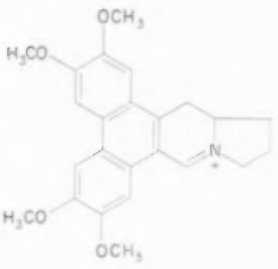


IV : R = H
IVa : R = CHO



V

The infra-red spectra of the synthetic (±) and natural (−) tylophorine were identical in chloroform soluton. The synthetic compound was further resolved through (+) camphorsulphonic acid into (−)tylophorine, m.p. 292°, $[\alpha]_D^{30}$ −11·5° and (+)tylophorine, m.p. 292°, $[\alpha]_D^{30}$ +12·25°. The (−)tylophorine was identical in every respect with natural tylophorine. The structure assigned to tylophorine has, therefore, been fully confirmed by the synthesis reported here.

EXPERIMENTAL

2,3,6,7-Tetramethoxy-9-hydroxymethylphenanthrene. Methyl 2,3,6,7-tetramethoxyphenanthrene. 9-carboxylate[3] (6 g) was added portionwise with stirring to a slurry of lithium aluminium hydride (2 g) in dry tetrahydrofuran (100 ml). Stirring was continued for 2 hr more. The complex was decomposed as usual and the organic layer separated and dried (Na_2SO_4). The solvent was distilled off and the residue, dissolved in chloroform, was passed through a column of alumina and then recrystallized from benzene to give the *alcohol* (4 g), m.p. 185° (Found: C, 69·8; H, 6·3. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%).

2,3,6,7-Tetramethoxy-9-chloromethylphenanthrene. The foregoing carbinol (1·4 g) dissolved in dry chloroform (50 ml) containing dry pyridine (1 ml) was treated with thionyl chloride (2 ml) in chloroform (10 ml) at 5°. The mixture was then gently warmed on a water bath for 1 hr and poured

into crushed ice. The chloroform layer was washed well with water, dil Na_2CO_3 solution and again with water and dried (Na_2SO_4). The solvent was removed and the residue recrystallized from benzene–petroleum ether (b.p. 40–60°) to give the *chloride* (1·2 g), m.p. 192° (Found: C, 66·0; H, 5·5. $C_{19}H_{19}O_4Cl$ requires: C, 65·8; H, 5·5%).

N-(2,3,6,7-*Tetramethoxyphenanthrylmethyl*)*prolinol* (II). The chloride (0·2 g) and prolinol[5] (0·3 g) were dissolved in dry toluene and refluxed with stirring for 20 hr. The toluene solution was then repeatedly extracted with dil HCl. The combined acid extract was shaken once with ether and then cooled and basified with liquor ammonia. The liberated base was thoroughly extracted with chloroform. The chloroform layer was washed well with water and dried (Na_2SO_4). The residue obtained after removal of the solvent was recrystallized from benzene to give the substituted *prolinol* (0·2 g), m.p. 220° (Found: C, 69·9; H, 6·8. $C_{24}H_{29}O_5N$ requires: C, 70·1; H, 7·1%).

2-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylmethyl*)*pyrrole* (III). To a mixture of magnesium (1·2 g) in dry ether (50 ml) was added dropwise a solution of ethyl bromide (5·5 g) in dry ether (30 ml). After stirring for 1 hr, the reaction vessel was cooled in ice and freshly distilled pyrrole (3·4 g) in dry ether (10 ml) was added dropwise and the stirring continued for 30 min more.

The above pyrrylmagnesium bromide was added dropwise to a solution of 2,3,6,7-tetramethoxy-9-chloromethylphenanthrene (2·5 g) in dry tetrahydrofuran (40 ml) with stirring. The stirring was continued for 3 hr and the complex was then decomposed with ice and a saturated solution of ammonium chloride. After decomposition, the whole was extracted with chloroform and the extract washed and dried (Na_2SO_4). The solvent was removed and the gummy residue passed through a column of acid-washed alumina in chloroform solution. The chloroform solution was evaporated and the residue recrystallized from benzene–petroleum ether (b.p. 40–60°) to give the *pyrrole* (1·8 g), m.p. 212° (Found: C, 73·1; H, 6·3. $C_{23}H_{23}O_4N$ requires: C, 72·8; H, 6·5%).

2-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylmethyl*)*pyrrolidine* (IV). The foregoing pyrrole (0·2 g) in acetic acid (30 ml) containing Adams catalyst (0·15 g) was shaken with hydrogen at a press of 60 lbs/in² for 12 hr, with the addition of fresh catalyst (0·05 g) at the end of 4 hr. The solution was filtered and evaporated to dryness *in vacuo*. The residue was taken up in H_2SO_4 (2 N; 20 ml) and the acid extract shaken with ether. The acid layer was cooled and made alkaline with aqueous NaOH and the base extracted with chloroform. The solvent was removed and the gummy residue (0·08 g) recrystallized from benzene–petroleum ether (b.p. 40–60°) to give the *pyrrolidine*, m.p. 152° (Found: C, 72·1; H, 7·0. $C_{23}H_{27}O_4N$ requires: C, 72·4; H, 7·1%).

N-*Formyl derivative of* IV (IVa). The above pyrrolidine (0·3 g) was treated with formic acid (98%; 1·5 ml) and heated gradually to 180° and then maintained at 180° for 1 hr. The residue was cooled and taken up in chloroform, washed with dil $NaHCO_3$ solution and then with water and dried (Na_2SO_4). The residue after removal of the solvent was crystallized from dry ether to give the N-*formyl derivative* (0·2 g), m.p. 140° (Found: C, 70·6; H, 6·6. $C_{24}H_{27}O_5N$ requires: C, 70·4; H, 6·6%).

(±)*Tylophorine* (I). The above formyl derivative (0·2 g) was refluxed in dry toluene (6 ml) with phosphorus oxychloride (0·5 ml) for 1 hr. It was then diluted with a large volume of pet ether (b.p. 40–60°) and the precipitated quaternary compound (V) was repeatedly washed with pet ether. The crude compound was dissolved in methanol (15 ml) and treated with sodium borohydride (0·2 g) and left overnight. The solvent was then removed *in vacuo* and the residue was decomposed with water and extracted with chloroform. The residue obtained after removal of the solvent was passed through a column of alumina in chloroform solution. It was then recrystallized from chloroform–ethanol to give (±)*tylophorine* (0·05 g), m.p. 292°. The infra-red spectra of the synthetic and natural tylophorine were identical in chloroform solution (Found: C, 73·0; H, 7·1. $C_{24}H_{27}O_4N$ requires: C, 73·3; H, 7·0%).

Resolution of (±)*tylophorine*. (±)Tylophorine (0·15 g) in chloroform (5 ml) was added to a solution of (+)camphorsulphonic acid (0·09 g) in chloroform (5 ml) and the mixture was evaporated to dryness. The residue was recrystallized from methanol (2·5 ml). The crystalline mass (50 mg), m.p. 295° was filtered and washed with a little methanol. It was found to be the l-base-d-salt having the rotation $[\alpha]_D^{30}$ +20° (*c*, 1·5; in $CHCl_3$). The filtrate was evaporated to dryness and the residue crystallized from chloroform–acetone to give the d-base-d-salt (40 mg), m.p. 285–287°, $[\alpha]_D^{30}$ +24·1° (*c*, 1·2; in $CHCl_3$). The base liberated from the l-base-d-salt had m.p. 292°(decomp), $[\alpha]_D^{30}$ −11·5°

[5] P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta* **31**, 1617 (1948).

c, 0·866; in $CHCl_3$). The base liberated from the d-base-d-salt had m.p. 292° (decomp), $[\alpha]_D^{30}$ +12·25° (*c*, 0·733; in $CHCl_3$).

Acknowledgements—We are thankful to Mr. S. Selvavinayakam for the microanalyses reported here and for the infra-red spectra of the compounds. Grateful acknowledgement is also made to the Government of India for the award of National Research Fellowships to two of us (M. V. L. and S. R.).

Tetrahedron, 1961, Vol. 14, pp. 288 to 295. Pergamon Press Ltd. Printed in Northern Ireland

CHEMICAL EXAMINATION OF *TYLOPHORA ASTHMATICA*—V[1]

STRUCTURE OF TYLOPHORININE[2]

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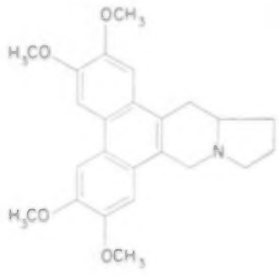
Abstract—Tylophorinine, the minor alkaloid of *Tylophora asthmatica*, has been oxidized to yield 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylic acid. A synthesis of the corresponding imide has been achieved. Desoxytylophorinine, obtained by hydrogenolysis of the alkaloid, has been synthesized. These results in conjunction with other degradation experiments have enabled the assignment of the structure XIV to tylophorinine.

THE isolation of the alkaloids of *Tylophora asthmatica* has been described previously.[3] The major alkaloid, tylophorine, has been shown to have structure I by degradation[4]



I

as well as by synthesis.[1] The present paper deals with the elucidation of the structure of the minor alkaloid, tylophorinine.

Tylophorinine is a powerfully vesicant compound, occurring to the extent of less than 0·001 per cent in the dried plant. Initial attempts to prepare the alkaloid in a pure form were not wholly successful, tylophorine being the usual contaminant. However, a preliminary chromatography of the base over alumina without undue exposure to light, followed by conversion to the hydrochloride and repeated crystallization of the latter gave a pure material. Although the base liberated from the hydrochloride could be crystallized from chloroform, satisfactory analyses on the base could not be obtained, there being evidently some decomposition, as indicated by

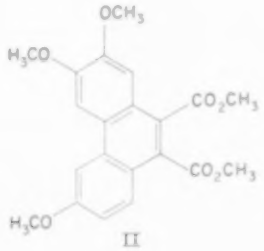
[1] Part IV: *Tetrahedron* **14**, 284 (1961).
[2] Parts of this work have been published in the form of brief notes: [a] T. R. Govindachari, B. R. Pai, S. Rajappa and N. Viswanathan, *Chem. & Ind.* 950 (1959); [b] T. R. Govindachari, B. R. Pai, I. S. Ragade, S. Rajappa and N. Viswanathan, *Ibid.* 966 (1960).
[3] T. R. Govindachari, B. R. Pai and K. Nagarajan, *J. Chem. Soc.* 2801 (1954).
[4] T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan and B. R. Pai, *Tetrahedron* **4**, 311 (1958); T. R. Govindachari, M. V. Lakshmikantham, B. R. Pai and S. Rajappa, *Ibid.* **9**, 53 (1960).

the deepening colour of the compound. On the basis of analyses of the hydrochloride, the formula of the base had to be revised from $C_{23}H_{27}O_4N$[3] to $C_{23}H_{25}O_4N$. Zeisel determination showed the presence of three methoxyls in the molecule. The ultraviolet absorption spectrum of tylophorinine (λ_{max} 258, 287, 340 mμ; log ε 4·61, 4·34, 2·91) was very similar to that of cryptopleurine[5] indicating that it was probably a 2,3,6-trimethoxyphenanthrene derivative.

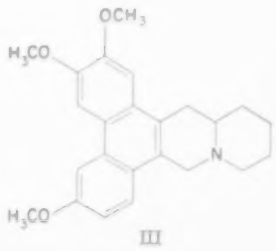
The fourth oxygen atom in the alkaloid was evidently present as an aliphatic hydroxyl group. The infra-red spectrum (nujol) of the base showed a band at 3·1 μ. Acetylation of tylophorinine yielded an acetate, $C_{25}H_{27}O_5N$, with infra-red absorption bands ($CHCl_3$) at 5·8 and 8·0 μ (—OCOMe). The U.V. spectrum of the base was unaffected by the addition of alkali, showing that the hydroxyl group was not phenolic.

Tylophorinine did not have an N-Me group and had no easily reducible unsaturation, but yielded a crystalline methiodide. Evidently tylophorinine is a tertiary base with nitrogen common to two rings as in tylophorine. With the intention of carrying out a series of reactions parallel to the successful degradation sequence in tylophorine, the alkaloid was subjected to both Hofmann and Emde reactions. However, the Hofmann degradation, carried out either by the pyrolysis of the methohydroxide, or by refluxing the methiodide with potassium t-butoxide in t-butanol, gave only a very meagre yield of a compound, whose analytical values were only in moderate agreement with the formula $C_{24}H_{27}O_4N$. Similarly the Emde degradation too gave a very small quantity of a base which was found to decompose spontaneously on keeping. Thus the extremely low yield in these degradation reactions precluded the possibility of the derivation of any useful information regarding the structure of the parent alkaloid.

Direct oxidation studies were however, more useful in the structural elucidation. Vigorous oxidation of tylophorinine methiodide gave *m*-hemipinic acid as the only isolable product. Mild oxidation of the methiodide yielded an imide, $C_{19}H_{15}O_5N$, and an acid which was converted to an anhydride (I.R. bands at 5·45 and 5·62 μ) under crystallization conditions. Methylation of the acid with diazomethane yielded a diester, $C_{21}H_{20}O_7$, m.p. 160–162°, identical with dimethyl 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylate (II) obtained similarly from the methiodide of cryptopleurine (III).* Since the structure of cryptopleurine itself has been rigorously established by X-ray crystallographic analysis[6] as well as by synthesis[7] the part structure (IV) for tylophorinine follows:



II



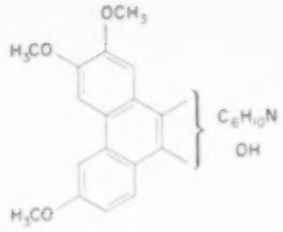
III

* We are extremely grateful to Dr. E. Gellert for a very generous gift of cryptopleurine.

[5] E. Gellert and N. V. Riggs, *Austral. J. Chem.* **7**, 113 (1954).

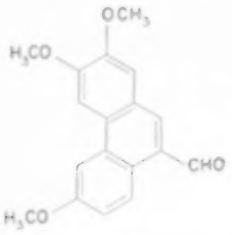
[6] J. Fridrichsons and A. Mathieson, *Nature, Lond.* **173**, 732 (1954).

[7] C. K. Bradsher and H. Berger, *J. Amer. Chem. Soc.* **80**, 930 (1958); P. Marchini and B. Belleau, *Canad. J. Chem.* **36**, 581 (1958).

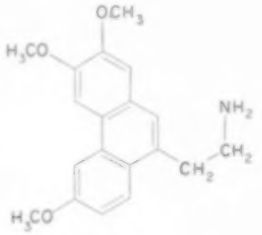


IV

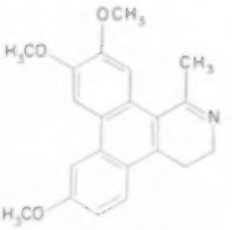
Simultaneously we had also undertaken the synthesis of the imide, $C_{19}H_{15}O_5N$, obtained in the oxidation of tylophorinine methiodide. 2,3,6-Trimethoxyphenanthrene-9-aldehyde (V), obtained by standard methods[8] from the corresponding acid[7] was converted to the amine (VI) through the nitrostyrene. Acetylation followed by cyclization yielded the dihydroisoquinoline (VII), whose methiodide, on oxidation,



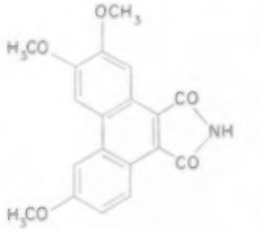
V



VI



VII



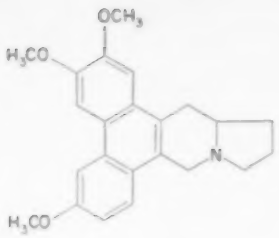
VIII

yielded 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylimide (VIII), identical with the degradation product (infra-red).

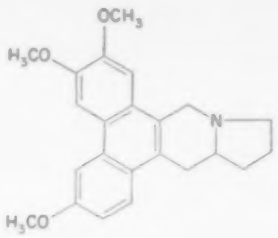
On the assumption that the heterocyclic portion of the molecule was similar to that in tylophorine, the location of the hydroxyl group was next investigated. Potentiometric titration of both tylophorinine hydrochloride as well as tylophorinine methiodide indicated that the base was not a carbinolamine. Catalytic hydrogenation of tylophorinine in acetic acid in the presence of palladium on charcoal and perchloric acid yielded desoxytylophorinine, $C_{23}H_{25}O_3N$, m.p. 252–254°, indicating the presence of a benzyl alcohol system in tylophorinine.

If tylophorinine were to contain a phenanthroindolizidine system as in tylophorine the desoxy derivative can have either of the two structures IX and X. The synthesis of

[8] J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.* 584 (1936).

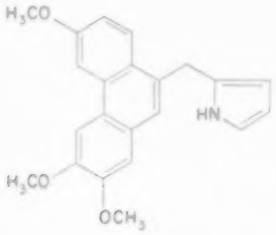


IX

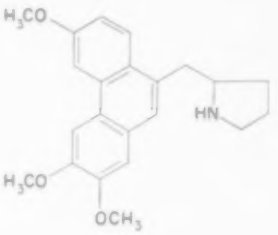


X

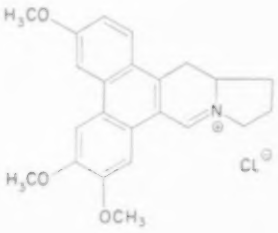
a structure corresponding to X was achieved as follows: Condensation of 2,3,6-trimethoxy-9-phenanthrylmethyl chloride[7] with pyrryl magnesium bromide gave 2-(2,3,6-trimethoxy-9-phenanthrylmethyl)pyrrole (XI), which was catalytically reduced to the pyrrolidine (XII). N-Formylation followed by cyclization gave the quaternary compound (XIII), which was reduced by sodium borohydride to 2,3,6-trimethoxy-phenanthro(9,10:7′,6′)indolizidine (X). The infra-red spectra of the synthetic compound and of desoxytylophorinine in chloroform solution were identical. The



XI



XII



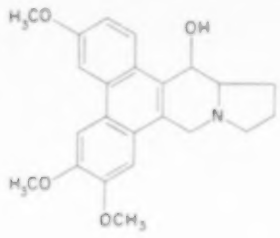
XIII

two compounds, on being subjected to the Hofmann degradation, gave in good yield the same methine, $C_{24}H_{27}O_3N$, m.p. 171·5° (identical m.p., mixed m.p., ultra-violet and infra-red spectra).

Since desoxytylophorinine is thus proved to be X, tylophorinine itself should be represented by XIV.

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured with a Beckmann Model DU Spectrophotometer. Infra-red spectra were measured by Mr. S. Selvavinayakam using a Perkin-Elmer Infracord Spectrophotometer.



XIV

Purification of tylophorinine

The crude alkaloidal material obtained by extraction of *Tylophora asthmatica*[3] was chromatographed in chloroform solution over alumina. The earlier fractions gave predominantly tylophorine. The later fractions had m.p. 235–245°. More of this material was obtained by elution of the column with chloroform containing 1% ethanol. This was rechromatographed in chloroform over alumina to get crude tylophorinine, m.p. 240–246°. The base was dissolved in chloroform, saturated with dry hydrogen chloride gas and the hydrochloride precipitated with dry ether. Three crystallizations of the product from ethanol gave pure *tylophorinine hydrochloride*, m.p. 257° (decomp); R_f 0·59 (n-butanol–water–acetic acid, 20:19:1) (Found: C, 66·6, 66·2; H, 6·2, 7·0; N, 3·3; OMe, 23·6, 20·6. $C_{23}H_{25}O_4N$. HCl requires: C, 66·4; H, 6·3; N, 3·4; 3 OMe, 22·4%). The base regenerated from the pure hydrochloride had m.p. 248–249° after crystallization from chloroform but satisfactory analyses could not be obtained for this due to decomposition. This base had λ_{max} 258, 287, 340 mμ (log ε 4·61, 4·34, 2·91). The yield of pure tylophorinine was about 0·001% based on the plant material used.

O-*Acetyltylophorinine*

Tylophorinine (100 mg) was heated on a water bath for 2 hr with acetic anhydride (2 ml) and a few drops of pyridine. The solution was cooled, diluted with water, basified with ammonia and extracted with ether. The residue from the ether layer after two crystallizations from benzene–pet ether (b.p. 40–60°) gave colourless needles of the *acetyl derivative* (30 mg), m.p. 222–223° (decomp) (Found: C, 71·0; H, 6·7. $C_{25}H_{27}O_5N$ requires: C, 71·3; H, 6·4%).

Tylophorinine methiodide

A solution of tylophorinine (0·5 g) in dry chloroform (100 ml) was refluxed for 3 hr on a water bath with methyl iodide (5 ml) and then left overnight. The solution was concentrated and the precipitated methiodide (0·6 g) was filtered off and washed with a little chloroform. It had m.p. 243–245° (decomp) but decomposed on crystallization from aqueous ethanol to give material, m.p. 240° (decomp), shrinking from 210°.

Oxidation of tylophorinine methiodide

(a) *Vigorous oxidation with potassium permanganate*. Tylophorinine methiodide (0·5 g) in water (150 ml) was treated with aqueous potassium permanganate (3%; 125 ml) with stirring at 30° and then at 100° till a faint pink colour persisted. The mixture was filtered and the manganese dioxide residue washed thoroughly with hot water. The filtrate was evaporated to dryness, acidified with dil H_2SO_4 and extracted continuously with ether for 12 hr. The extract was dried (Na_2SO_4) and evaporated. The residue was sublimed *in vacuo* (0·02 mm) at 170–200°. The sublimate was dissolved in ethanol (5 ml) and treated with ethylamine (1·5 ml). The solution was evaporated and the residue treated again with ethanolic ethylamine. The solvents were evaporated and the residue heated at 180° for 5 min and sublimed *in vacuo* at 150–160°. The sublimate (20 mg) on crystallization from ethanol had m.p. 190–215°. Chromatography in benzene over alumina followed by crystallization from ethanol gave N-ethyl-*m*-hemipinimide (5 mg) as colourless needles, m.p. and mixed m.p. 230–231°. Its ultraviolet and infra-red absorption spectra were also identical with those of the synthetic specimen.

The mother liquors from the above crystallization gave only a small amount of intractable product.

(b) *Mild oxidation with potassium permanganate.* A solution of tylophorinine methiodide (0·5 g) in pyridine (10 ml) and water (10 ml) was treated with stirring over a period of 3 hr with aqueous potassium permanganate (N/10; 220 ml), first at 30° and then at 40–45°. The manganese dioxide residue was filtered off, washed with water, dried and extracted in a Soxhlet with chloroform for 5 hr. The fluorescent chloroform solution was evaporated and the residue crystallized twice from pyridine to give yellow needles of 2,3,6-*trimethoxyphenanthrene*-9,10-*dicarboxylimide* (20 mg), m.p. 297°, identical in all respects with a synthetic sample (see below). (Found: C, 67·2; H, 5·0; $C_{19}H_{15}O_5N$ requires; C, 67·7; H, 4·5%). λ_{max} 260, 285, 315, 405 mμ (log ε 4·37, 4·11, 3·89 and 3·65).

The aqueous alkaline filtrate from the oxidation was evaporated *in vacuo* to 5 ml and acidified with conc HCl. The precipitated acid (0·25 g) was filtered, washed with water and dried. On recrystallization from acetic acid, yellow needles (80 mg) of the anhydride, m.p. 240–250° (decomp) were obtained. The anhydride (30 mg) was suspended in methanol and treated with ethereal diazomethane (from 3 g of nitrosomethylurea). After 24 hr the solvents were evaporated and the residue crystallized twice from methanol to give pale yellow needles of *dimethyl* 2,3,6-*trimethoxyphenanthrene*-9,10-*dicarboxylate* (12 mg), m.p. 160–162°. (Found: C, 65·5; H, 5·7; OMe, 40·7. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2; 5 OMe, 40·4%). λ_{max} 265, 285, 330 mμ (log ε 4·58, 4·44 and 3·98). It was identical (mixed m.p., ultra-violet and infra-red spectra) with a sample made similarly by oxidation of cryptopleurine methiodide. 0·5 g of the methiodide gave, after oxidation and esterification, 20 mg of the diester. The ester was purified easily by chromatography in benzene over alumina. (Found: C, 65·6; H, 5·3%).

Synthesis of 2,3,6-*trimethoxyphenanthrene*-9,10-*dicarboxylimide*

(a) 2,3,6-*Trimethoxyphenanthrene*-9-*carboxylic acid hydrazide.* Ethyl 2,3,6-trimethoxyphenanthrene-9-carboxylate[7] (5 g) in amyl alcohol (50 ml) was refluxed for 4 hr with hydrazine hydrate (98%; 14 ml). The hydrazide separated on cooling. Ethanol (100 ml) was added and the mixture filtered warm. Crystallization from a large excess of ethanol gave needles of the *hydrazide* (5 g), m.p. 236° (decomp). (Found: C, 66·8; H, 5·7. $C_{18}H_{18}N_2O_4$ requires: C, 66·3; H, 5·5%).

(b) N-*Benzenesulphonyl*-2,3,6-*trimethoxyphenanthrene*-9-*carboxylic acid hydrazide.* Benzenesulphonyl chloride (7 g) was added dropwise with stirring to a suspension of the hydrazide (5 g) (previously dried at 110° for 5 hr *in vacuo*) in dry pyridine (150 ml) at 0°. The mixture was left overnight and then poured into ice and hydrochloric acid. The precipitated solid was collected and crystallized from ethanol to give the *benzenesulphonyl derivative* (5 g), m.p. 240° (decomp) (Found: C, 61·7; H, 5·1. $C_{24}H_{22}N_2SO_6$ requires: C, 61·8; H, 4·7%).

(c) 2,3,6-*Trimethoxyphenanthrene*-9-*aldehyde.* The above sulphonyl derivative (1 g), powdered and dried at 140° for several hours *in vacuo*, was treated in ethylene glycol suspension (10 ml) at 160°, with stirring, with anhydrous sodium carbonate (1 g). After 80 sec warm water was added. The mixture was cooled and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and evaporated and the residue crystallized from acetic acid giving the aldehyde (0·3 g) as pale yellow needles, m.p. 161° (Found: C, 73·2; H, 5·6. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

(d) 2,3,6-*Trimethoxy*-9-2′-*nitrovinylphenanthrene.* The aldehyde (1 g) in acetic acid (5 ml) was refluxed with nitromethane (2 ml) and ammonium acetate (0·5 g) for 2 hr. The contents were cooled and poured on ice. The gum that separated was washed with water and crystallized from acetic acid to give the *nitrovinylphenanthrene* (0·5 g) as orange plates, m.p. 192° (decomp) (Found: C, 67·4; H, 4·7. $C_{19}H_{17}O_5N$ requires: C, 67·2; H, 5·0%).

(e) 2,3,6-*Trimethoxy*-9-2′-*aminoethylphenanthrene.* The nitrovinylphenanthrene (0·7 g) in dry tetrahydrofuran (25 ml) was added to a well-stirred solution of lithium aluminium hydride (0·7 g) in tetrahydrofuran (30 ml). The mixture was stirred for 3 hr, left overnight and then decomposed as usual with ether and water. The ether–tetrahydrofuran extract was evaporated, the residue taken up in ether and extracted with dil HCl. The acid extract was basified and the base extracted with benzene. The benzene extract was washed with water, dried (Na_2SO_4) and the solvent removed to give the base as an uncrystallizable gum. The *picrate* crystallized from acetic acid as red needles, m.p. 235° (decomp) (Found: C, 55·5; H, 4·6. $C_{25}H_{24}O_{15}N_4$ requires: C, 55·5; H, 4·4%).

(f) 2,3,6-*Trimethoxy*-9-2′-*acetamidoethylphenanthrene.* The crude base obtained from 0·7 g of the nitrovinylphenanthrene was heated on a steam bath for 3 hr with acetic anhydride (2 ml) and

pyridine (1 ml). The contents were cooled, poured on ice and left aside for 1 hr. The solid that separated was filtered, washed with water and crystallized from ethyl acetate–ethanol to give the *acetamide* (0·3 g), m.p. 215° (Found: C, 71·7; H, 6·4. $C_{21}H_{23}O_4N$ requires: C, 71·4; H, 6·5%).

(g) *The dihydroisoquinoline* (VII). The acetamide (0·3 g) was heated on a steam bath with phosphorous oxychloride (7 ml) for 3 hr. The contents were cooled, poured into ice with shaking and left aside to decompose excess phosphorous oxychloride. More water was added and the contents warmed to dissolve the amine hydrochloride completely. The solution was extracted twice with benzene to remove any unreacted amide, basified and the liberated base extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4) and distilled. The residue obtained as an oil on removing the chloroform was without purification converted into the *methiodide* which crystallized from methanol as yellow needles, m.p. 239° (Found: C, 55·3; H, 5·0. $C_{22}H_{24}O_3NI$ requires: C, 55·4; H, 5·0%).

(h) 2,3,6-*Trimethoxyphenanthrene*-9,10-*dicarboxylimide*. The above methiodide (320 mg) in pyridine (2 ml) and water (25 ml) was treated dropwise with stirring with aqueous potassium permanganate solution (2%; 65 ml). Sulphur dioxide was passed into the contents to dissolve the manganese dioxide. The solution was extracted with chloroform, the chloroform solution washed with alkali, then with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed in chloroform over alumina. The imide, m.p. 296–297°, crystallized from pyridine–ethanol, was identical with the sample obtained by oxidation of tylophorinine methiodide (mixed m.p., ultra-violet and infra-red absorption spectra).

Hofmann degradation of tylophorinine

(a) *With silver oxide*. Tylophorinine methiodide (0·4 g) in water (50 ml) was shaken for 4 hr with freshly precipitated silver oxide (from 5 g silver nitrate). The solution was filtered, evaporated to dryness *in vacuo* and the residue heated at 0·5 mm for 30 min on a steam bath. The product was extracted with benzene and chromatographed in benzene solution over alumina. Elution with benzene containing 0·5% ethanol gave *tylophorinine methine* (20 mg), needles from benzene–pet ether (b.p. 40–60°), m.p. 196–197° (Found: C, 72·7; H, 6·4. $C_{21}H_{21}O_4N$ requires: C, 73·3; H, 6·9%). λ_{max} 260, 285, 315, 345, 360 mμ (log ε 4·73, 4·58, 4·05, 3·18 and 2·66).

(b) *With potassium t-butoxide*. Tylophorinine methiodide (0·2 g) was added to a solution of potassium (100 mg) in dry t-butanol (30 ml) and refluxed in an atmosphere of nitrogen for 14 hr on a water bath. The solvent was evaporated *in vacuo*, the residue diluted with water and extracted with chloroform. The chloroform solution was dried and the solvent removed. The residue, on purification, gave tylophorinine methine (25 mg), m.p. and mixed m.p. 196–197°.

Emde degradation of tylophorinine

Tylophorinine methiodide (0·2 g) was refluxed with silver chloride (from 1 g of silver nitrate) in water (10 ml) and ethanol (10 ml) for 5 hr and left overnight. The mixture was filtered and the filtrate boiled to remove the alcohol. To the hot aqueous solution was added sodium amalgam (5%; 25 g) over a period of 3 hr. The solution was further heated on a steam bath for 5 hr and left overnight. The product was extracted with benzene, the benzene solution dried (Na_2SO_4) and distilled. The residue was chromatographed in benzene over alumina. The first 20 ml of the eluate gave a small amount of gummy material. The subsequent 50 ml gave the *Emde base* (20 mg), needles from benzene–pet ether (b.p. 40–60°), m.p. 161–162° (Found: C, 73·4; H, 7·7. $C_{21}H_{29}O_4N$ requires: C, 72·9; H, 7·3%). λ_{max} 260, 285, 345, 360 mμ (log ε 4·40, 4·31, 2·90 and 2·57).

Desoxytylophorinine

Tylophorinine (0·2 g) in acetic acid (20 ml) containing perchloric acid (70%; 0·2 ml) was shaken with palladized charcoal (5%; 0·2 g) in presence of hydrogen at 23 lbs/in² at 55–60° for 1 hr. The solution was filtered from the catalyst and the solvent removed *in vacuo*. The product was basified with ammonia and extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and distilled and the residue chromatographed in chloroform over alumina. The product was crystallized twice from chloroform–methanol to give *desoxytylophorinine* (100 mg), m.p. 252–254° (decomp), $[\alpha]_D^{30}$ −3·7° (in $CHCl_3$) (Found: C, 76·1; H, 7·1. $C_{23}H_{25}O_3N$ requires: C, 76·0; H, 6·9%). λ_{max} 255, 290, 340 mμ (log ε 4·55, 4·31 and 3·25).

Hofmann degradation of desoxytylophorinine

Desoxytylophorinine (100 mg) in chloroform (20 ml) was refluxed with excess methyl iodide for 2 hr and left overnight. The solvent and excess of methyl iodide were distilled off, the residue triturated with water and the solid methiodide filtered. The methiodide in water (15 ml) was shaken with silver oxide (from 1 g of silver nitrate) for 4 hr. The mixture was filtered and the filtrate evaporated at 50° *in vacuo*. The residue was heated at 100° at 0·5 mm for 1 hr. The product was extracted with hot benzene and the material obtained crystallized twice from benzene–pet ether (b.p. 40–60°) to yield *desoxytylophorinine methine* (25 mg), m.p. 171·5° (Found: C, 76·0; H, 7·0. $C_{24}H_{27}O_3N$ requires: C, 76·4; H, 7·2%). λ_{max} 260, 285, 340 mμ (log ε 4·86, 4·59 and 3·32).

Synthesis of desoxytylophorinine

(a) 2-(2,3,6-*Trimethoxy*-9-*phenanthrylmethyl*)*pyrrole*. To ethylmagnesium bromide (prepared from 0·9 g magnesium) in dry ether (30 ml) was added, under nitrogen and with stirring, freshly distilled pyrrole (2·5 g). The contents were stirred for 5–10 min after the addition was completed. The homogeneous complex formed was taken in a dropping funnel and added dropwise to a well-stirred solution of 2,3,6-trimethoxy-9-phenanthrylmethyl chloride[7] (2 g) in tetrahydrofuran (25 ml) cooled in ice. After stirring for 3 hr in an atmosphere of nitrogen, the reaction mixture was decomposed with saturated ammonium chloride solution. Sufficient chloroform was added and the layers separated. The chloroform extract was washed with water, dried (Na_2SO_4) and the solvent evaporated. The residue was extracted with boiling benzene and the benzene soluble material chromatographed in chloroform over acid-washed alumina. The product crystallized from benzene–pet ether (b.p. 40–60°) to give 2-(2,3,6-*trimethoxy*-9-*phenanthrylmethyl*)*pyrrole* (0·9 g), m.p. 203° (Found: C, 75·8; H, 6·2. $C_{22}H_{21}O_3N$ requires: C, 76·0; H, 6·0%).

(b) 2-(2,3,6-*Trimethoxy*-9-*phenanthrylmethyl*)*pyrrolidine*. The above pyrrole (0·6 g) in acetic acid (30 ml) was reduced with Adams catalyst (0·15 g) at a hydrogen pressure of 50 lbs/in^2. After shaking for 3 hr more of the catalyst (0·1 g) was added. After shaking overnight, the solution was filtered from the catalyst and the solvent removed *in vacuo*. The residue was extracted thrice with 4 N H_2SO_4. The acid extract was extracted once with ether and then basified with sodium hydroxide. The white precipitate that separated was extracted with chloroform, the chloroform layer washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed in chloroform over alumina. Crystallization of the product from benzene–pet ether (b.p. 40–60°) gave the *pyrrolidine* (0·23 g), as plates, m.p. 140° (Found: C, 75·3; H, 7·1. $C_{22}H_{23}O_3N$ requires: C, 75·2; H, 7·1%).

(c) 2,3,6-*Trimethoxyphenanthro*(9,10:7′,6′)*indolizidine* (= -*desoxytylophorinine*). A mixture of the above pyrrolidine (0·225 g) and formic acid (98%; 1·5 ml) was heated gradually to 180° and maintained at that temp for 90 min. The cooled reaction product was taken up in chloroform, washed successively with $NaHCO_3$ solution, dil HCl and water. The dried (Na_2SO_4) extract was concentrated to a small bulk and chromatographed over alumina in chloroform. The formyl derivative thus obtained (140 mg) could not be crystallized. It was cyclized as such by refluxing with phosphorus oxychloride (3 ml) and toluene (6 ml) for 90 min. Sufficient pet ether (b.p. 40–60°) was added to the cooled contents to precipitate the chloride and the supernatant liquid was decanted off. The oily chloride was washed repeatedly with pet ether (b.p. 40–60°), dried *in vacuo* and reduced with sodium borohydride (0·3 g) in methanol (10 ml). The methanol was removed *in vacuo*, the residue taken up in chloroform, washed with water, dried (Na_2SO_4), concentrated to a small bulk and chromatographed over alumina in chloroform. Crystallization of the product from chloroform–methanol yielded 2,3,6-*trimethoxyphenanthro*(9,10:7′,6′)*indolizidine* (70 mg), as needles, m.p. 213–214° (Found: C, 75·8; H, 6·9. $C_{22}H_{25}O_3N$ requires: C, 76·0; H, 6·9%).

(d) *Hofmann degradation of* 2,3,6-*trimethoxyphenanthro*(9,10:7′,6′)-*indolizidine*. The above base (60 mg) was converted into the methiodide and subjected to the Hofmann degradation as in the case of natural desoxytylophorinine to yield the *methine* (30 mg), needles from benzene–pet ether (b.p. 40–60°), m.p. 171·5°, undepressed by admixture with a sample of natural desoxytylophorinine methine. Their ultra-violet as well as infra-red absorption spectra were identical. (Found: C, 76·7; H, 7·4. $C_{24}H_{27}O_3N$ requires: C, 76·4; H, 7·2%).

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THE STRUCTURE AND SYNTHESIS OF XANTHOMICROL*

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Abstract—Xanthomicrol is shown to be 5,4'-dihydroxy-6,7,8-trimethoxyflavone by a combination of physical and degradative methods. Its synthesis from pentamethoxybenzene is described.

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YERBA BUENA (*Satureia douglassii*, formerly *Micromeria chamissonis*) is a ground growing, evergreen vine of the mint family (Labiatae) which is widespread along the western coast of the United States. In 1908 Power and Salway[1] isolated from it in 0·02 per cent yield a yellow crystalline material which they named xanthomicrol. They assigned to it the formula $C_{15}H_{10}O_4$-$(OH)_2$ on the basis of its analysis and the formation of a diacetate. As this formula is that of a dihydroxydimethoxyxanthone we felt that the substance deserved further investigation as part of our continuing study of natural xanthones.

Xanthomicrol was isolated by a simplified route involving the extraction of dried, defatted yerba buena with ether. Crude xanthomicrol could be obtained directly by extraction from the ether solution with dilute sodium carbonate. Purification was effected by chromatography on acid-washed alumina.

The ultraviolet spectra of xanthomicrol (Table 1) and its derivatives suggested very strongly that they were not xanthones and the possibility was eliminated by examination of the NMR spectrum of the diacetate. This showed not only the expected two acetyl methyl peaks at $\tau = 7{\cdot}59$, 7·73, but also three peaks of similar height at $\tau = 5{\cdot}95$, 6·02, 6·17, proving that xanthomicrol is a trimethoxy rather than the anticipated dimethoxy compound. This result was supported by the NMR spectra of xanthomicrol monomethyl ether, prepared by reaction with diazomethane, and the dimethyl ether, prepared with methyl sulphate and potassium hydroxide. These spectra indicated strongly the presence of four and five methoxyl groups respectively.

These findings cast serious doubt on the molecular formula proposed by Power and Salway as the removal of nine hydrogens as methoxyl and two as hydroxyl leaves the compound embarrassingly poor in hydrogen. The elemental analyses obtained for xanthomicrol and its derivatives could be fitted best, however, by the assumption of a formula $C_{15}H_5O_2(OCH_3)_3(OH)_2$, i.e. one corresponding to a dihydroxytrimethoxyflavone. The suggestion of a flavone nucleus was confirmed by the demethylation of xanthomicrol with hydriodic acid, followed by acetylation to give trisnorxanthomicrol pentaacetate, whose ultraviolet spectrum was essentially that of flavone[2] (Table 1).

* Presented in part at the International Symposium on the Chemistry of Natural Products, Melbourne, August 1960.

[1] F. B. Power and A. H. Salway, *J. Amer. Chem. Soc.* **30**, 251 (1908).

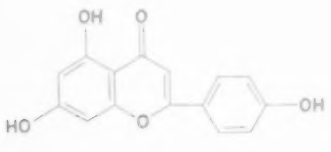
[2] T. A. Geissmann, *Modern Methods of Plant Analysis* (Edited by K. Paech and M. V. Tracey) Vol. 3, p. 487ff. Springer Verlag, Berlin (1955).

TABLE 1. ULTRAVIOLET SPECTRA OF XANTHOMICROL DERIVATIVES

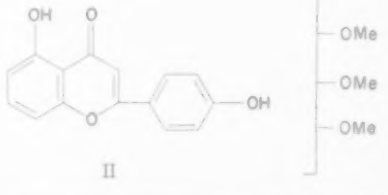
	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε
Xanthomicrol (VI)	282	18,900	296	18,000	336	24,700
5,4′-Dihydroxy-6,7,8-trimethoxy-flavone* (VI)	283	18,600	296	18,200	335	25,100
Trisnorxanthomicrol pentaacetate	258	16,900	301	18,800		
Flavone[2]	250	11,800	297·5	16,000		
Monomethylxanthomicrol (VII)	285	21,200	295	21,600	332	24,800
4′-Benzyloxy-5-hydroxy-6,7,8-tri-methoxyflavone (X)	286	22,000	296	24,400	332	26,700
Dimethylxanthomicrol (VIII)	272	20,200			324	28,200
5,6,7,8,4′-pentamethoxy-flavone (VIII)*	272	19,900			324	28,600
4′-Benzyloxy-5,6,7,8-tetra-methoxyflavone (IX)	272	19,600			325	29,600
Xanthomicrol diacetate	270	25,800	308	21,800		

* Synthetic

Xanthomicrol and its demethylation product give strongly yellow, non-fluorescent solutions when treated with boroacetic anhydride,[3] suggesting the presence of a free hydroxyl group in the 5 position, but the absence of an oxygen substituent at C-3[4]. The solubility in dilute sodium carbonate solution places the other hydroxyl group in the 4′ or 7 position.[5] The hydroxyl groups were assigned by examining the changes produced in the ultraviolet and visible spectra of xanthomicrol and monomethyl-xanthomicrol when their alcoholic solutions were made ca. 0·002 M in hydroxide ion. The shifts produced were effectively identical with those reported by Nordstrom *et al.*[6] for derivatives of apigenin (I) having free hydroxyl groups at the 4′ and 5 positions respectively. The ionization of xanthomicrol at the 4′ hydroxyl as well as the ready formation of a monomethyl ether is explained by the well known lack of reactivity of strongly chelated hydroxyl groups such as the one at C-5.[7] On this basis the partial structure (II) may be written for xanthomicrol.



I



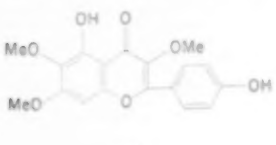
II

Micro base fusion of xanthomicrol and paper chromatography of the products gave as the major product a compound whose R_f values in two solvents and whose

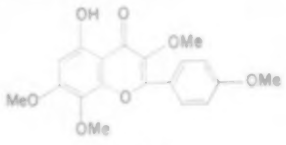
[3] O. Dimroth and T. Faust, *Ber. Dtsch. Chem. Ges.* **54,** 3020 (1921); O. Dimroth, *Leibigs Ann.* **446,** 97 (1926).
[4] E. Rodd (Editor), *The Chemistry of Carbon Compounds* Vol. IV B, p. 910. Elsevier, Amsterdam (1956).
[5] *Inter al.* L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 3136 (1951).
[6] G. H. Mansfield, T. Swain and C. G. Nordstrom, *Nature, Lond.* **172,** 23 (1953).
[7] S. Wawzonek, *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 2, p. 265. John Wiley, New York (1951).

color reactions were identical with those of *p*-hydroxybenzoic acid but different from all other phenolic acids tested, including vanillic and syringic. The same substance was formed by the micro ozonolysis of xanthomicrol diacetate followed by mild hydrolysis with aqueous alcoholic base. Thus it could be shown that the p-hydroxybenzoic acid did not arise by demethylation during the base fusion and the spectral assignment of a hydroxyl to C-4′ was confirmed.

If the B ring of xanthomicrol contains no methoxyl groups, then only the four structures derived from II by addition of methoxyls to three of the positions 3, 6, 7, or 8 are possible. Three of these may be eliminated. Xanthomicrol and its diacetate differ in melting points and spectra from penduletin[8] (III); monomethylxanthomicrol in melting point and ultraviolet spectrum from flindulatin[9] (IV); and dimethylxanthomicrol in melting point from 3,5,6,8,4′-pentamethoxyflavone[10] (V). The remaining possibility (VI) is not a flavonol and is consistent with the color tests with boroacetic anhydride, the observation that xanthomicrol does not give a pink color with magnesium and hydrochloric acid in ethanol and the similarity of the melting point of xanthomicrol dimethyl ether (152·5–155°) and those recorded for the naturally occurring pentamethoxyflavone tangeretin (VIII) (153–154°).[11]



III



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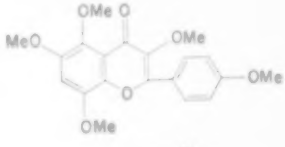
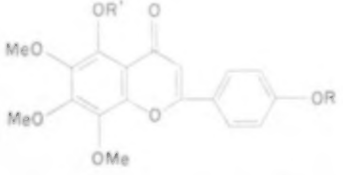


V



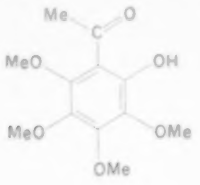
VI R = R′ = H
VII R = Me, R′ = H
VIII R = R′ = Me
IX R′ = Me, R = $CH_2\phi$
X R′ = H, R = $CH_2\phi$

Xanthomicrol has been synthesized as a confirmation of the structure (VI). Pentamethoxybenzene was prepared from pyrogallol by the method of Baker[12] and was acylated with acetyl chloride and aluminium chloride in ether. Baker reports that this reaction gives 2-hydroxy-3,4,5,6-tetramethoxyacetophenone (XI) in 27 per cent yield. We have found that when the reaction mixture is warmed, it produces a mixture of products, the major one of which is not (XI) but rather 2,6-dihydroxy-3,4,5-trimethoxyacetophenone (XII). Vapor-phase chromatography of the crude base-soluble material from the acylation showed the presence of at least two components, and chromatography on acid-washed alumina separated the mixture into (XI) and (XII) together with small amounts of other products. The pure (XI) was a yellow oil which was identified by its NMR spectrum, which showed separate peaks corresponding to one acetyl and four methoxyl groups. No aromatic hydrogen could

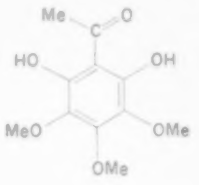
[8] S. E. Flores and J. Herran, *Tetrahedron* **2**, 308 (1958).
[9] R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 181 (1954).
[10] K. J. Balakrishna and T. R. Seshadri, *Proc. Indian Acad. Sci.* **27A**, 260 (1948).
[11] E. K. Nelson, *J. Amer. Chem. Soc.* **56**, 1392 (1944); L. J. Goldsworthy and R. Robinson, *Chem. & Ind.* 47 (1957).
[12] W. Baker, *J. Chem. Soc.* 662 (1941).

be found, but the hydroxyl appeared at an extremely unshielded position ($\tau = -2{\cdot}69$) characteristic of strong intramolecular hydrogen bonds.[13]

The new product (XII) crystallized as yellow needles. The structure was proved by the remarkable simplicity of its NMR spectrum and that of its acetate. Both of these compounds showed two extremely sharp methoxyl peaks in the ratio 2:1 and the acetate showed an equally sharp acetate peak also of height 2. Such a spectrum can only be explained on the basis of the symmetrical structure (XII). In addition, the hydroxyl peak was shifted upfield to $\tau = 0{\cdot}14$, as might be expected if there is a rapid averaging of the hydrogen-bonded and non-hydrogen-bonded hydroxyl protons.



XI



XII

XIII R = —CHO

XIV R = —C(=O)Cl

The formation of (XII) is an example of an unusual bisdealkylation under very mild conditions. It is normally assumed that aluminium chloride in ether will demethylate only one alkoxyl group *ortho* to an acyl group on a benzene ring. Indeed, such a reaction was used in very satisfactory yield in the syntheses leading to pentamethoxybenzene. The double demethylation leading to (XII) appears to be without precedent and may perhaps be caused by the buttressing effect of the groups in the 3 and 5 positions.[14]

p-Benzyloxybenzaldehyde (XIII) was condensed with (XI) using sodium hydride in tetrahydrofuran. The more common base for chalcone syntheses, 50 per cent sodium hydroxide in ethanol, appeared to be less satisfactory. The intermediate chalcone was oxidized with selenium dioxide[15] in amyl alcohol to give 4′–benzyloxy-5,6,7,8-tetramethoxyflavone (IX) whose ultraviolet spectrum was essentially identical with that of dimethylxanthomicrol. Simultaneous debenzylation and 5-demethylation of (IX) with aluminium chloride in ether gave xanthomicrol in 35 per cent yield from (XI).

To avoid the need for selective demethylation at C-5 an alternative route was explored in which (XII) was esterified with *p*-benzyloxybenzoyl chloride (XIV) and the crude ester treated with sodium hydride in tetrahydrofuran. The β-diketone produced by this reaction[16] was not isolated but was cyclized smoothly by brief treatment with warm 98 per cent formic acid to give 4′-benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (X) which showed a U.V. spectrum markedly different from (IX) but very similar to that of methylxanthomicrol. Debenzylation now could be performed under the milder conditions of HCl in acetic acid to give xanthomicrol in 48 per cent yield.

[13] Compare *o*-hydroxyacetophenone $\tau = -2{\cdot}13$.
[14] W. J. Horton and J. T. Spence, *J. Amer. Chem. Soc.* **80**, 2453 (1958).
[15] H. S. Mahal, H. S. Rai and K. Venkataraman, *J. Chem. Soc.* 866 (1935).
[16] Ref. 7, p. 233.

The occurrence of a flavone with the structure shown for xanthomicrol in a member of the Labiatae is of some interest. Heretofore, flavones, as distinct from flavonols, totally oxygenated in ring A, have been found only in various members of the genus Citrus, e.g. tangeretin[11] nobiletin[17] and desmethylnobiletin.[18] Now there appears in xanthomicrol a new member of this group, closely related to tangeretin but produced by a totally different botanical family.

EXPERIMENTAL

All melting points were taken on a Kofler block. Infrared spectra were taken in chloroform on a Perkin–Elmer Model 21 and ultraviolet spectra on a Cary Model 11 or Model 14 in ethanol. NMR spectra were taken in carbon tetrachloride or carbon tetrachloride–chloroform on a Varian 60 mc instrument and are given as τ values[19] measured from an internal tetramethylsilane reference. Numbers in parentheses represent estimated relative intensities. Combustion analyses are by Drs. Weiler and Strauss, Oxford, and Dr. A. Bernhardt, Mulheim.

Isolation of xanthomicrol (VI)

Samples of *Micromeria chamissonis* were gathered near Seattle during the summer months. During this period the time of gathering did not appear to affect the yields. The whole plant was dried with forced air at 52°C, ground in a Wiley mill, and defatted by extraction in a Soxhlet with petroleum ether (30–60°).

Defatted, ground plant material (2050 g) was extracted in a Soxhlet with ether for 18 hr. The extracts were concentrated to ca. 500 ml, stored in the icebox overnight, and filtered. The filtrate was washed with dilute sodium bicarbonate and then extracted with 1/3 saturated Na_2CO_3 solution (6 × 60 ml). The extracts were filtered, acidified, and extracted with ether which was dried and evaporated to give 1·31 g of dark crystalline material.

This was chromatographed on 13 g of acid-washed alumina and eluted with CH_2Cl_2–ether to give 553 mg of xanthomicrol. One crystallization from methanol gave pure xanthomicrol (314 mg 0·015%). M.p. 227–230°. U.V.: λ_{max} mμ (ε): 282 (18,900), 296 (18,000), 336 (24,700); in 0·002 N NaOH/EtOH, 276 (15,100), 402 (32,500). I.R.: 3·08, 6·07, 6·26, 6·32, 6·43 μ (Nujol). (Found: C, 62·44; H, 4·77; CH_3O, 26·85. $C_{15}H_7O_4(OCH_3)_5$ requires: C, 62·79; H, 4·68; CH_3O, 27·02%).

Methylation of xanthomicrol with diazomethane: monomethylxanthomicrol (VII)

Xanthomicrol (94 mg) was dissolved with heating in methanol (ca. 20 ml), cooled in ice, and treated with excess diazomethane in ether. The reaction mixture was cooled in an ice bath for 2 hr and the excess diazomethane decomposed by glacial acetic acid, added dropwise. The solution was evaporated to give crude product which was chromatographed on acid-washed alumina. Benzene–dichloromethane (4:1) and dichloromethane eluted monomethylxanthomicrol (47 mg, 48%). Crystallization from ethyl acetate–hexane gave long yellow needles, m.p. 180–181°. U.V.: λ_{max} mμ (ε): 285(21,200), 295(21,600), 332(24,800); in 0·002 N NaOH/EtOH, 302(29,100), 395(6,900). NMR: 6·13(1), 6·07(2), 5·94(1)τ. (Found: C, 63·76; H, 5·01. $C_{19}H_{18}O_7$ requires: C, 63·68; H, 5·06%).

Methylation of xanthomicrol with methyl sulfate: dimethylxanthomicrol (VIII)

Xanthomicrol (85 mg) in acetone (2 ml) was treated alternately with portions of methyl sulfate (1 g) and potassium hydroxide solution (3 g of 30% aqueous base.) Acetone (1 ml) was added and the mixture heated on the steam bath for 1½ hr. The mixture was cooled and water added. The crystalline product was filtered off, washed and dried to give dimethylxanthomicrol (74 mg, 80%). Crystallization from dichloromethane–cyclohexane gave pale yellow needles, m.p. 153–156°. U.V.: λ_{max} mμ (ε): 272(20,200), 324(28,200). NMR: 6·15(1), 6·10(2), 6·03(1), 5·97(1)τ. (Found: C, 64·75; H, 5·51. $C_{20}H_{20}O_7$ requires: C, 64·51; H, 5·41%).

[17] R. Robinson and K. F. Tseng, *J. Chem. Soc.* 1004 (1938).
[18] P. S. Sarin and T. R. Seshadri, *Tetrahedron* **8**, 64 (1960).
[19] G. V. D. Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

Xanthomicrol diacetate

Xanthomicrol (56 mg) was treated with acetic anhydride (0·6 ml) and pyridine (0·7 ml) at room temperature for 23 hr. Water was added and the product extracted with ether, which was washed with dilute acid, base, and water and dried over sodium sulfate. Evaporation of solvent and crystallization from cyclohexane–dichloromethane gave xanthomicrol diacetate (40 mg, 57%) as white needles, m.p. 126·5–128·5°. U.V.: λ_{max} mμ (ε): 270(25,800), 308(21,800). NMR: 7·73 (1), 7·59(1), 6·17(1), 6·02(1), 5·59(1)τ. (Found: C, 61·60; H, 4·94. $C_{22}H_{20}O_9$ requires: C, 61·68; H, 4·71%).

Trisnorxanthomicrol pentaacetate

Xanthomicrol (44 mg) was refluxed with 48% HI (2 ml) for 3 min. The solid first dissolved and then crystallized again. The mixture was poured into water, $NaHSO_3$ was added, and the solution was extracted with ether, ethyl acetate, and 1-butanol. Some solid remained; the aqueous solution was decanted and the residue was dissolved in methanol and added to the combined extracts. These were washed with water and dilute sodium bicarbonate, and then evaporated to give crystalline orange-yellow product (31 mg) dec. > 300°. U.V. maxima 302 and 340 mμ. Treatment with boro-acetic anhydride gave a strongly yellow-orange, non-fluorescent solution.

The crude product was acetylated with acetic anhydride (2 ml) and pyridine (0·5 ml) on the steam bath for 35 min. The reaction mixture was poured into water and the product crystallized. Recrystallization from hexane–dichloromethane gave 27 mg of pentaacetate (41%). For analysis this was crystallized twice from ethanol to give fine white needles with a double m.p., 220–229° and 235–246° unchanged on drying in high vacuum. U.V.: λ_{max} mμ (ε); 258(16,900), 301(18,800). (Found: C, 58·88; H, 3·93; CH_3CO, 40·0. $C_{15}H_9O_7(CH_3CO_2)_5$ requires: C, 58·60; H, 3·93; CH_3CO, 42·0%).

Base fusion of xanthomicrol

Xanthomicrol (14 mg) was heated at 260° for 15 min in a mixture of potassium and sodium hydroxide (0·4 g each) and a few drops of water. The reaction mixture was cooled, acidified with dilute sulfuric acid and extracted with ether, which was dried ($MgSO_4$) and evaporated to give a dark oil containing some crystals. Paper chromatography using BuOH:H_2O:Conc. NH_3 (4:5:1) as a solvent gave a yellow spot R_f 0·14 when sprayed with *p*-nitrobenzene diazonium fluoroborate as well as other minor spots. When i-PrOH:H_2O:Conc. NH_3 (8:1:1) was used as the solvent the same spot appeared at R_f 0·24. Parallel runs with *p*-hydroxybenzoic acid gave a spot at the same R_f's and with the same color in both solvents.

Ozonolysis of xanthomicrol diacetate

Xanthomicrol diacetate (48 mg) was dissolved in 1:1 CH_2Cl_2:EtOAc and cooled in a Dry Ice-acetone bath. A slow stream of ozone in oxygen was passed in for 1½ hr until a faint blue color developed in the solution. The reaction mixture was treated with potassium iodide in methanol and acetic acid, poured into water containing enough sodium bisulfite to reduce the iodine, and extracted with ethyl acetate. The extract was evaporated to give 38 mg of crude product which was dissolved in ethanol (5 ml) and 10% aqueous sodium hydroxide (5 ml) and allowed to stand overnight under nitrogen. Acidification and filtration gave xanthomicrol (21 mg). The filtrate was extracted with ether (2 × 5 ml), which was in turn extracted with dilute sodium bicarbonate (2 × 5 ml). Acidification and back extraction into ether gave on evaporation 4 mg of acidic material. When this was chromatographed on paper using the same systems as the base fusion products, the same yellow spot corresponding to *p*-hydroxybenzoic acid was observed on development with *p*-nitrobenzene-diazonium fluoroborate.

Pentamethoxybenzene[10]

Pentamethoxybenzene was synthesized from pyrogallol by the procedure of Baker. The overall yield was 34%.

2-Hydroxy-3,4,5,6-tetramethoxyacetophenone (XI) *and 2,6-dihydroxy-3,4,5-trimethoxyacetophenone* (XII)

Anhydrous ether (220 ml) was added to anhydrous aluminum chloride (44 g), while the system

was cooled efficiently in an ice-salt bath. Pentamethoxybenzene (44 g) was added in one portion, then acetyl chloride (44 g) dropwise over 15 min. The solution was heated to 25°; a gentle spontaneous reaction set in. The solution was stirred for 14 hr at room temperature, and heated at reflux for 2 hr. Water (310 ml) and concentrated hydrochloric acid (46 ml) were added cautiously. After evaporation of the ether on the steam bath the hot solution was stirred for 3 hr. The reaction mixture was cooled and extracted with dichloromethane (325 ml). The organic solution was extracted with 10% sodium hydroxide (650 ml). The basic solution was acidified and extracted with dichloromethane, which was washed with water, dried over anhydrous sodium sulfate and evaporated to yield crude acetophenone (19·9 g, 40·3%) as a rust-colored oil.

VPC analysis of the crude product with a silicone on firebrick column at ca. 245° showed the presence of at least two components, retention times 5 and 6·5 min.

A portion of the crude oil (4·99 g) was chromatographed on Merck acid-washed alumina (100 g). Carbon tetrachloride and benzene eluted a yellow oil [0·71 g; 14%; retention time (246°), 5 min], which was considered to be 2-hydroxy-3,4,5,6-tetramethoxyacetophenone (XI). I.R.: 6·15 (*s*), 6·30 (*m*), 6·78, 6·88, 6·93 μ. U.V.: λ_{max} mμ (ε): 282(10,450), 347(2600). NMR: 7·42(3), 6·30(3), 6·27(3), 6·13(3), 6·05(3), and −2·69(1)τ. Continued elution with dichloromethane–ether gave a partially crystalline fraction which on crystallization from petroleum ether gave a bright yellow crystalline substance m.p. 86–88° [0·83 g; 17%; retention time (242°), 6·7 min]. This was assigned the structure 2,6-dihydroxy-3,4,5-trimethoxyacetophenone (XII). I.R.: 2·90, 6·17, 6·71, 6·88 μ. U.V.: λ_{max} mμ 283(14,300), 356(2850). NMR: 7·37(3), 6·22(6), 5·99(3), 0·14(2)τ. (Found: C, 54·97; H, 6·09. $C_{11}H_{14}O_6$ requires: C, 54·54; H, 5·83%).

Acetylation with excess acetic anhydride and pyridine on the steam bath gave the diacetate as a colorless oil which could not be crystallized. NMR: 7·80(2), 7·70(1), 6·20(2), 6·10(1)τ.

Investigation of other fractions by VPC indicated considerable additional amounts of XII, but still mixed with XI from which it could not be crystallized.

For the separation of larger amounts of material, the procedure given below was found to be convenient.

The crude acetophenone mixture (8·2 g) was dissolved in ether (75 ml), washed with dilute sodium bicarbonate, and extracted with 10% sodium carbonate (Frac. I, 1 × 100 ml; Frac. II, 2 × 60 ml). The extracts were acidified, extracted with ether, the ethereal solutions evaporated, and the residue taken up in hot petroleum ether to leave behind a small amount of dark residue. From Fraction I (3·40 g), 2,6-dihydroxy-3,4,6-trimethoxyacetophenone (1·64 g; 20%) was isolated by crystallization from ligroin. VPC showed Fraction II (1·59 g) to be a 1:1 mixture of the two acetophenones. The carbonate insoluble fraction (2·31 g) was chromatographed on acid-washed alumina. Elution with petroleum ether gave nearly pure (by VPC) 2-hydroxy-3,4,5,6-tetramethoxyacetophenone [1·9 g; 22%; retention time (240°), 5·5 min].

4′-Benzyloxy-5,6,7,8-tetramethoxyflavone (IX)

2-Hydroxy-3,4,5,6-tetramethoxyacetophenone (701 mg), *p*-benzyloxybenzaldehyde (638 mg), sodium hydride (263 mg.), and tetrahydrofuran (8 ml) were flushed with oxygen-free nitrogen and refluxed for 4 hr in a nitrogen atmosphere. The mixture was poured onto ice and extracted with ether (5 × 30 ml), which was freed of base, dried over anhydrous sodium sulfate and evaporated to give crude 2′-hydroxy-3′,4′,5′,6′,-tetramethoxy-4-benzyloxychalcone as an orange oil (1·11 g). U.V.: 292 mμ (shoulder), 360 mμ. I.R.: 6·13, 6·22, 6·40μ.

The chalcone (1·11 g) and fresh selenium dioxide (1·43 g) were refluxed in n-amyl alcohol (16·5 ml) for 19½ hr. The hot solution was filtered from the free selenium and steam distilled to remove the n-amyl alcohol. The residue was extracted with dichloromethane, which was washed with 5% sodium hydroxide (2 × 25 ml). The organic layer was freed of base, dried and evaporated to give 1·24 g brown tar. Chromatography on Merck alumina gave on elution with ether 4′-benzyloxy-5,6,7,8-tetramethoxyflavone (388 mg, 35%) which was recrystallized from dichloromethane–cyclohexane, m.p. 144–145°. U.V.: λ_{max} mμ (ε): 272(19,600), 325(29,600). (Found: C, 69·58; H, 5·57. $C_{20}H_{20}O_7$ requires: C, 69·63; H, 5·39%).

4′,5-Dihydroxy-6,7,8-trimethoxyflavone (VI)

4′-Benzyloxy-5,6,7,8-tetramethoxyflavone (55 mg) was dissolved in a solution of anhydrous

aluminium chloride (335 mg) in anhydrous ether (1·4 ml) and refluxed for 10 hr. Water (10 ml), ether (5 ml) and concentrated hydrochloric acid (0·5 ml) were added and refluxing was continued for ¾ hr. The organic layer was separated and the aqueous layer extracted thoroughly with ether. The ether solutions were washed with dilute hydrochloric acid, sodium carbonate and 5% sodium hydroxide. The sodium carbonate solution was acidified and extracted with ether to give 42 mg 5,4′-dihydroxy-6,7,8-trimethoxyflavone (99%). Crystallization from EtOAc gave material (m.p. 224–229°) identical with natural xanthomicrol in all respects: I.R. and U.V. curves were superimposable; mixed m.p. was not depressed.

p-*Benzyloxybenzoyl chloride* (XIV)

p-Benzyloxybenzoylchloride was prepared fresh for every reaction by treating *p*-benzyloxybenzoic acid[20] with about five times its weight of thionyl chloride, refluxing for 15 min, and removing the excess thionyl chloride *in vacuo*. The whole crude acid chloride was then used for esterification.

4′-*Benzyloxy*-5-*hydroxy*-6,7,8-*trimethoxyflavone* (X)

The acid chloride was prepared from 1·5 g of *p*-benzyloxybenzoic acid and added to 2,6-dihydroxy-3,4,5-trimethoxyacetophenone (660 mg) in 5 ml of benzene and 1 ml of pyridine. After refluxing 25 min the mixture was poured into water and worked up by extraction with ether and washing with dil H_2SO_4 and dil $NaHCO_3$ to give 1·811 g of crude ester as a dark yellow oil. This was refluxed 7 hr in dry tetrahydrofuran (15 ml) with 370 mg of sodium hydride and then added to dilute sulfuric acid. The product was extracted with ether, the ether evaporated, and the residue cyclized with 98% formic acid on the stream bath for 5 min. The addition of water gave a copious crystalline precipitate which was crystallized from ethanol-dichloromethane to give 596 mg of 4′-benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (56%) m.p. 155–158°. An analytical sample melted 158–159·5°. U.V.: λ_{max} (ε), 286(22,000), 296(22,400), 332(26,700). (Found: C, 69·35; H, 5·32. $C_{25}H_{22}O_7$ requires: C, 69·12; H, 5·07%).

Debenzylation of 4′-*benzyloxy*-5-*hydroxy*-6,7,8-*trimethoxyflavone*

4′-Benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (100 mg), glacial acetic acid (5 ml) and concentrated hydrochloric acid (1 ml) were heated on a steam bath for 2½ hr. The solution was allowed to cool to room temperature, and water (35 ml) was added. Filtration gave a yellow crystalline product (82 mg, m.p. 177–217°), which was dissolved in ether and extracted exhaustively with half-saturated sodium carbonate solution. Acidification of the basic solution, extraction with ether and evaporation of the solvent gave 5,4′-dihydroxy-6,7,8-trimethoxyflavone (67 mg, 85%). The material, recrystallized from benzene, melted at 222–224°; mixed m.p. with xanthomicrol undepressed. U.V.: λ_{max} mμ (ε): 283(18,600), 296(18,200), 335(25,100). I.R.: identical with natural xanthomicrol.

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[20] J. B. Cohen and H. W. Dudley, *J. Chem. Soc.* **97**, 1746 (1910).

Tetrahedron, 1961, Vol. 14, pp. 304 to 309. Pergamon Press Ltd. Printed in Northern Ireland

THIOPEGAN DERIVATIVES—XVI

SYNTHESIS OF 10:11-THIOPEGAN DERIVATIVES CONTAINING A SATURATED THIAZOLE MOIETY AND OF THEIR RELATED COMPOUNDS

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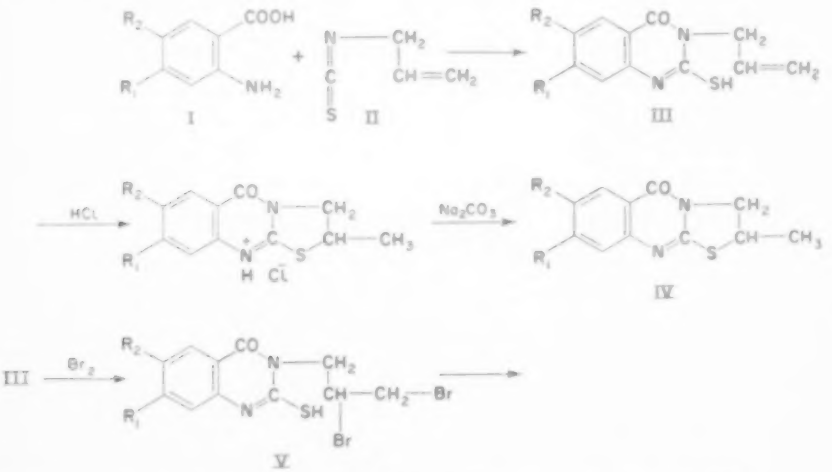
Abstract—2-Methyl-6-chloro-10:11-thiopegene-9:4-one, 2:7-dimethyl-10:11-thiopegene-9:4-one and the corresponding methylene bases have been synthesized. These methylene thiopegans furnish corresponding isomeric 2-methyl derivatives on acid treatment. 2-Bromomethyl-7-methyl-10:11-thiopega-2:9-diene-4-one has been condensed with piperidine and diethylamine to incorporate the therapeutically important basic moiety in these compounds. New routes to the synthesis of various substituted 2-methyl-10:11-thiopegans and 2-bromomethyl-10:11-thiopega-2:9-diene-4-ones have been developed with a view to improve their yields.

THIS paper constitutes an extension and continuation of the previous work.[1,2] 6-Chloro and 7-methyl thiopegan derivatives containing saturated thiazole moiety and their related compounds have been synthesized with a view to study the effect of the chloro and methyl groups in these positions on the biological properties of the thiopegan ring system. The initiating reaction employs the condensation between allyl isothiocyanate and the requisite anthranilic acid followed by a series of operations, sequentially represented as under:



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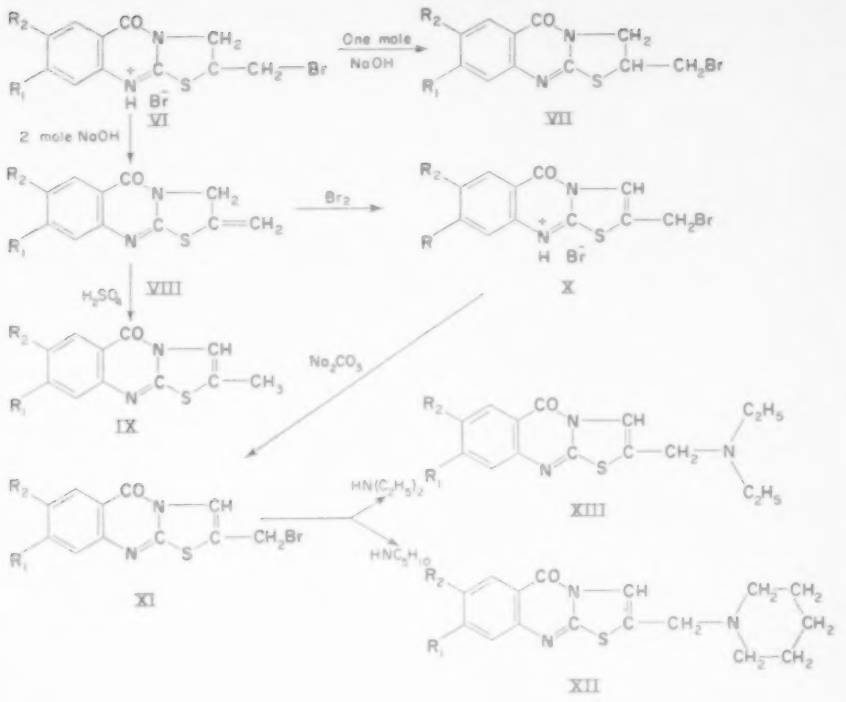
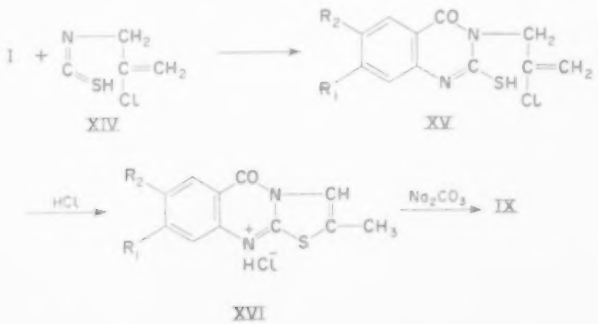
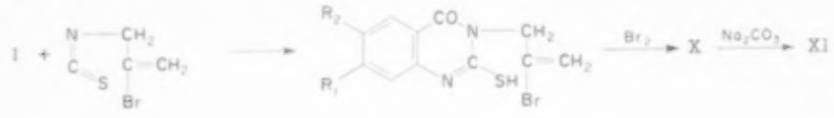
[1] K. S. Dhami *et al.*, *J. Sci. and Ind. Res.* **15,** 690 (1956).
[2] K. S. Dhami *et al.*, *J. Sci. and Ind. Res.* **16,** 311 (1957).



A simpler and superior pathway for the synthesis of 2-methyl-10:11-thiopegans (IX) was eventually developed which completes the synthetic scheme in fewer steps and better overall yield. The initiating reaction employs a new variant i.e. β-chloroallyl-isothiocyanate (XIV) in the aforementioned condensation with anthranilic acid. The resulting 3-(2-chloroallyl)-4-keto-2-mercapto-tetrahydroquinazolines (XV) underwent smooth cyclization to 2-methyl-10:11-thiopegan derivatives (XVI) with dry hydrochloric acid gas in boiling acetic acid solution. The direct ring closure involving dehydrochlorination of the intermediate (XV) was not observed in the initiating stage which apparently is due to the restricted mobility of the chlorine atom. The following explain the reaction sequence:



2-Bromomethyl-10:11-thiopega-2:9-diene-4-one reported earlier (X, $R_1 = R_2 =$ H) has been prepared in 28 per cent yield which is better than that obtained by the previous route (14·1 per cent), by a variation involving the condensation between β-bromoallyl isothiocyanate (XVII) with anthranilic acid (I) followed by the bromination of the intermediate tetrahydro derivative (XVIII) and subsequent basification of the bromo-compound (X) thus obtained; the course of various reactions is represented as follows:



XVIII

EXPERIMENTAL PROCEDURE

5-Chloroanthranilic-Acid Series

3-Allyl-6-chloro-4-keto-2-thio-tetrahydroquinazoline (III, $R_1 = H$, $R_2 = Cl$)

A mixture of 5-chloroanthranilic acid (33 g) and allyl-isothiocyanate (17·5 g) (prepared by refluxing 22 g allyl bromide and 19·5 g potassium thiocyanate in 10 ml ethanol for 30 min) was heated in an oil bath. A vigorous reaction ensued at 100°C and the reaction mixture was kept at this temperature for about 30 minutes when it began to solidify. It was then maintained at 110–115°C for 6 hr when practically all of it became solid. Crystallization from acetic acid (norit) furnished light pale rectangular needles, m.p. 237°C (18 g, 40%). (Found: S, 12·7. $C_{11}H_9ON_2SCl$ requires: S, 12·67%).

6-Chloro-2-methyl-10:11-thiopegene-9,4-one (IV; R_1—H; R_2—Cl)

Dry hydrochloric acid was passed through are fluxing solution of (III, $R_1 = H$; $R_2 = Cl$) (5 g) in glacial acetic acid (75 ml) for 6 hr. The residue obtained after evaporating off the solvent, was basified with sodium carbonate solution. After collecting and washing with water, the product was crystallized from alcohol (norit) in fine colourless rectangular plates, m.p. 146° (3 g, 60%). (Found: S, 12·38; $C_{11}H_9ON_2SCl$ requires: S, 12·67%).

Hydrochloride of the above base was obtained by saturating a solution of the substance in ethylmethyl ketone with dry hydrochloric acid gas. The product was crystallized from ethylmethyl ketone in fine colourless needles, m.p. 228° (74%). (Found: N, 9·40. $C_{11}H_{10}ON_2SCl_2$ requires: N, 9·68%).

2-Bromomethyl-6-chloro-10-11-thiopegene-9:4-one-hydrobromide (VI; $R_1 = H$; $R_2 = Cl$) *and the free base* (VII; $R_1 = H$; $R_2 = Cl$)

Bromine (3 ml) dissolved in glacial acetic acid (15 ml) was slowly added to a solution of (III; $R_1 = H$; $R_2 = Cl$) (15 g) in acetic acid (170 ml) at 45°, accompanied with thorough shaking of the reaction mixture. A fine pale yellow solid separated out instantaneously on the addition of the bromine solution. The reaction mixture was cooled and the product was collected under suction which on crystallization from glacial acetic acid furnished colourless compound, m.p. 288°, yield being 17·5 g (73%) (Found: S, 7·57. $C_{11}H_9ON_2SBr_2Cl$ requires: S, 17·7%).

Sodium hydroxide (1%) (0·0044 mole, 17·6 ml) was added to a solution of the above hydrobromide (0·0044 mole, 1·8 g) in 60% ethanol (40 ml) at 40°. The low melting solid obtained on cooling, was crystallized from dilute ethanol (norit) in white rectangular plates (0·82 g), m.p. 144°. (Found: N, 8·45. $C_{11}H_9ON_2SBrCl$ requires: N, 8·5%).

6-Chloro-2-methylene-10:11-thiopegene-9:4-one (VIII; $R_1 = R_2 = Cl$)

The hydrobromide (VI; $R_1 = H$; $R_2 = Cl$) (20 g, 0·06 mole) was dissolved in 70% ethanol (350 ml) and to this was added 2% sodium hydroxide solution (240 ml) (0·12 mole) at 45°. A white flocculent precipitate separated out instantaneously. This was collected after cooling and crystallized

from 60% ethanol as long rectangular needles, m.p. 193° (9 g, 70%). (Found: N, 11·2. $C_{11}H_7ON_2SCl$ requires: N, 11·15%).

Isomerization of (VIII, $R_1 = H$; $R_2 = Cl$) *to* 6-*chloro*-2-*methyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (IX: $R_1 = H$; $R_2 = Cl$). Methylene base (1 g) was dissolved in concentrated sulphuric acid (25 ml) at 8°. After about 5 min it was poured into crushed ice when a white solid separated out. It was collected after 30 min and washed with water. Crystallization from dilute ethanol furnished colourless slender needles, m.p. 206° (0·67 g, 67%). (Found: N, 10·6. $C_{11}H_7ON_2SCl$ requires: N, 11·1%).

Bromination of (VIII; $R_1 = H$; $R_2 = Cl$)-2-*Bromomethyl*-6-*chloro*-10:11-*thiopega*-2:9-*diene*-4-*one hydrobromide* (X; $R_1 = H$; $R_2 = Cl$)

Bromine (1 ml) dissolved in glacial acetic acid (7 ml) was added during 25 min to a solution of the methylene base (5 g) in acetic acid (95 ml) at 55°. A fine orange coloured solid (6·5 g) obtained on keeping was crystallized from glacial acetic acid (norit) as colourless product which melted at 272° with decomposition. (Found: N, 7·05, S, 7·85. $C_{11}H_8ON_2SBr_2Cl$ requires: N, 7·0; S, 8·0%).

6-*Chloro*-2-*piperidinemethyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (XII; $R_1 = H$; $R_2 = Cl$)

A solution of (XI; $R_1 = H$; $R_2 = Cl$) (0·002 mole, 0·75 g) in ethanol (45 ml) and piperidine (0·004 mole; 0·405 ml) was refluxed for 3 hr. The residue obtained after the distillation of the solvent was crystallized from ethanol as light pale needles, m.p. 193° (0·43 g, 44%). (Found: S, 9·55. $C_{16}H_{15}ON_2SCl$ requires: S, 9·6%).

2-*Bromomethyl*-6-*chloro*-10:11-*thiopega*-2:9-*diene*-4-*one* (XI; $R_1 = H$; $R_2 = Cl$)

The above hydrobromide (3 g) was thoroughly triturated with sodium carbonate solution. The pale yellow product was collected and washed with water. Crystallization from dilute ethanol furnished fine pale yellow needles (1·6 g, 66·3%) m.p. 202°. (Found: N, 8·16. $C_{11}H_6ON_2SBrCl$ requires: N, 8·5%).

6-*Chloro*-2-*diethylaminomethyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (XIII, $R_1 = H$, $R_2 = Cl$)

A solution of the bromobase (XI; $R_1 = H$; $R_2 = Cl$) (1 g, 0·003 mole) in ethanol (60 ml) and diethylamine (0·006 mole, 0·61 ml) was refluxed for 4 hr. The solvent was distilled off and the residue crystallized from 90% ethanol which deposited (0·55 g, 46%) white rectangular needles, m.p. 136°. (Found: N, 13·0. $C_{15}H_{16}ON_2SCl$ requires: N, 13·04%).

4-Methyl Anthranilic Acid Series

The experimental conditions employed are almost the same as in the case of 5-chloroanthranilic acid series.

3-*Allyl*-4-*keto*-7-*methyl*-2-*thio*-*tetrahydroquinazoline* (III; $R_1 = CH_3$; $R_2 = H$)

Crystallized from glacial acetic acid in colourless rectangular plates m.p. 233° (44%). (Found: N, 11·91. $C_{12}H_{12}ON_2S$ requires: N, 12·06%).

2:7-*Dimethyl*-10:11-*thiopegene*-9,4-*one* (IV; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in fine colourless rectangular plates, m.p. 144° (50%). (Found: N, 11·9; S, 13·68. $C_{12}H_{12}ON_2S$ requires: N, 12·1; S, 13·9%).

Hydrochloride of the base was obtained in 90% yield from glacial acetic acid as a colourless product melting at 264°. (Found, N, 10·2, S, 11·8. $C_{12}H_{13}ON_2SCl$ requires: N, 10·4; S, 11·9%).

2-*Bromomethyl*-7-*methyl*-10:11-*thiopegene*-9:4-*one*-*hydrobromide* (VI; $R_1 = CH_3$; $R_2 = H$)

Crystallized from glacial acetic acid (norit) as a colourless product m.p. 320° (d) (55%). (Found: N, 6·96; Br, 38,75. $C_{12}H_{12}ON_2SBr_2$ requires: N, 7·14; Br, 40·0%)

2-*Bromomethyl*-7-*methyl*-10:11-*thiopegene*-9:4-*one* (VII; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in white needles, m.p. 125° (80%). (Found: Br, 25·85. $C_{12}H_{11}ON_2SBr$ requires: Br, 25·72%).

2-*Methylene*-7-*methyl*-10:11-*thiopegene*-9:4-*one* (VII; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in long rectangular plates m.p. 189° (70%). (Found: N, 12·0. S, 13·95; $C_{12}H_{10}ON_2S$ requires: N, 12·17; S, 13·91%).

2:7-*Dimethyl*-10:11-*thiopegene*-2:9-*diene*-4-*one* (IX; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol in long slender needles m.p. 200° (75%) (Found: N, 12·1, S, 13·47. $C_{12}H_{11}ON_2S$ requires: N, 12·17; S, 13·9%).

Bromination of (VIII; $R_1 = CH_3$; $R_2 = H$); 2-*bromomethyl*-7-*methyl*-10:11-*thiopega*-2:9-*diene*-4-*one hydrobromide* (X; $R_1 = CH_2$; $R_2 = H$)

Crystallization from glacial acetic acid furnished colourless solid melting at 311–312° (d) (73%). (Found: N, 6·94; Br, 40·8. $C_{12}H_{10}ON_2SBr_2Cl$ requires: N, 7·2; Br, 41·0%).

2-*Bromomethyl*-7-*methyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (XI; $R_1 = CH_2$; $R_2 = H$)

Crystallized from ethanol in light yellow needles, m.p. 210° (83%). (Found: N, 8·57. $C_{12}H_9ON_2SBr$ requires: N, 9·0%).

2-*Diethylaminomethyl*-7-*methyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (XIII; $R_1 = CH_3$; $R_2 = H$)

Crystallized from dilute ethanol (norit) in colourless needles, m.p. 125° (50%). (Found: N, 14·2, $C_{14}H_{18}ON_2S$ requires: N, 13·95%).

Synthesis of various 2-*methyl*-10:11-*thiopega*-2:9-*diene*-4-*ones by the alternate route*

The initial reaction between β-chloroallyl isothiocyanate and various anthranilic acids was carried out under conditions identical with those for allyl isothiocyanate.

3-(2′-*Choroallyl*)-2-*mercapto*-4-*keto*-*tetrahydroquinazoline* (XV, $R_1 = R_2 = H$)

Crystallized from ethanol in fine needles, m.p. 191° (27%). (Found: N, 11·1; Cl, 13·8 $C_{11}H_9ON_2SCl$ requires: N, 11·1; Cl, 14·1%).

2-*Methyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (IX; $R_1 = R_2 = H$)

Crystallized from ethanol as a colourless compound m.p. 183° (25%). Mixed m.p. with (IX; $R_1 = R_2 = H$) as obtained by the isomerization of 2-methylene-10:11-thiopegene-9,4-one,[1] (XIII, $R_1 = R_2 = H$) gave no depression.

3-(2′-*Chloroallyl*)-2-*mercapto*-4-*keto*-6-*methyl tetrahydroquinazoline* (XV; $R_1 = H$; $R_2 = CH_3$)

Crystallization from glacial acetic acid furnished rectangular needles, m.p. 228° (32%). (Found: N, 10·8, Cl, 13·6. $C_{12}H_{11}ON_2SCl$ requires: N, 10·9; Cl, 13·7%).

2:6-*Dimethyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (IX; $R_1 = H$; $R_2 = CH_3$)

Crystallized from dilute ethanol in fine colourless slender needles m.p. 168° (40%). This was identical with the compound obtained by the isomerization of 2-methylene-6-methyl-10:11-thiopegene-9,4-one[2] (VIII; $R_1 = H$; $R_1 = CH_3$) as confirmed through undepressed m.m.p.

6-*Chloro*-3-(2′-*chloroallyl*)-2-*mercapto*-4-*keto*-*tetrahydroquinazoline* (XV; $R_1 = H$; $R_2 = Cl$)

Crystallization from glacial acetic acid furnished sulphur yellow product m.p. 222° (27%). (Found: N, 9·7; Cl, 24·8. $C_{11}H_8ON_2SCl_2$ requires: N, 9·76; Cl, 25·5%).

6-*Chloro*-2-*methyl*-10:11-*thiopega*-2:9-*diene*-4-*one* (IX; $R_1 = H$; $R_2 = Cl$)

Crystallized from dilute ethanol (norit) in long rectangular needles m.p. 206° (69%). This was found to be identical with (IX; $R_1 = H$; $R_2 = Cl$) obtained earlier through undepressed mixture m.p.

3-(2′-*Bromoallyl*)-2-*mercapto*-4-*keto*-*tetrahydroquinazoline* (XVIII; $R_1 = R_2 = H$)

Crystallized from alcohol in colourless light yellow needles m.p. 198° (50%). (Found: S, 11·0; Br, 26·9. $C_{11}H_9ON_2SBr$ requires: S, 10·79; Br, 26·9%).

2-Bromomethyl-10:11-thiopega-2:9-diene-4-one hydrobromide (X; $R_1 = R_2 = H$)

Crystallized from glacial acetic acid as a colourless product m.p. 295° (84%). (Found: S, 8·61; Br, 42·8. $C_{11}H_9ON_2SBr_3$ requires: S, 8·0; Br, 42·5%).

2-Bromomethyl-10:11-thiopega-2:9-diene-4-one (X, $R_1 = R_2 = H$)

The above hydrobromide was triturated with sodium carbonate solution. The residue was crystallized from alcohol as colourless solid m.p. 210° (30%). Mixed m.p. determination proved its identity with 2-bromomethyl-10:11-thiopega-2:9-diene-4-one obtained earlier.[1]

3-Allyl-6-chloro-4-keto-2-thio-tetrahydroquinazoline, 2-methyl-6-chloro-10:11-thiopegene-9;4-one-hydrochloride, 2-Methylene-6-chloro-10:11-thiopegene-9;4-one and 2-methyl-6-chloro-10:11-thiopega-2:9-diene-4-one were found active against St. haemolyticus at a dilution of 1:1000, 1:5000, 1:1000 and 1:1000 respectively.

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SYNTHESIS OF DITERPENES—IV[1]

METHYL (±)-DESISOPROPYLDEHYDROABIETATE

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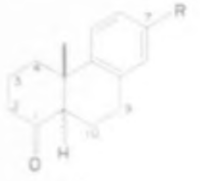
(*Received* 25 *February* 1961)

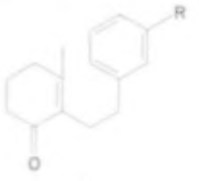
Abstract—The tricyclic ketone (I; R = H) has been synthesized by a new method, and converted into the bromo-ketone (XVII; R = Br). Favorskii rearrangement of the latter gave methyl (±)-desisopropyldehydroabietate (XX).

KETONES of the type I are synthetically readily available from phenethylcyclohexenones (II);[2,3,4] and their obvious potentialities for diterpene synthesis have stimulated work on the conversion of a carbonyl function into characteristic diterpenoid *gem*-groupings.[3,5] Applied to the tricyclic ketone (I; R = H), however, such investigations have led only to the *cis*-fused acids, (III)[6] and its C(1)-epimer.[7]

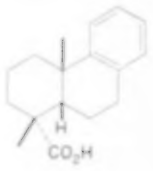
It is now well known that the introduction of angular groupings into fused systems increases the stability of a *cis*-compound relative to its *trans*-isomer.[8] Thus, although the ketone (IV) is approximately 80 per cent *trans* at equilibrium,[9] the ketone (I; R = Pr^i) from dehydroabietic acid is predominantly *cis* (ca. 60 per cent).[10] The



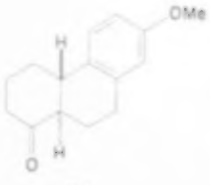
I



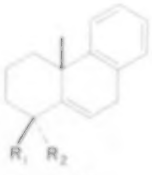
II



III



IV



V

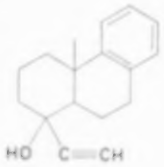
VI

[1] Part III: D. B. Bigley, N. A. J. Rogers and J. A. Barltrop, *J. Chem. Soc.* 4613 (1960).
[2] G. Stork and A. Burgstahler, *J. Amer. Chem. Soc.* **73**, 3544 (1951).
[3] N. N. Saha, P. N. Bagchi and P. C. Dutta, *Chem. & Ind.* 1143 (1954).
[4] N. N. Saha, P. N. Bagchi and P. C. Dutta, *J. Amer. Chem. Soc.* **77**, 3408 (1955).
[5] W. Parker and R. A. Raphael, *J. Chem. Soc.* 1723 (1955); U. R. Ghatak, N. N. Saha and P. C. Dutta, *Chem. & Ind.* 51 (1957); *J. Amer. Chem. Soc.* **79**, 4487 (1957).
[6] N. N. Saha, B. K. Ganguly and P. C. Dutta, *Chem. & Ind.* 412 (1956); *J. Amer. Chem. Soc.* **81**, 3670 (1959).
[7] U. R. Ghatak, D. K. Datta and S. C. Ray, *J. Amer. Chem. Soc.* **82**, 1728 (1960).
[8] *Inter al.* R. B. Turner, *J. Amer. Chem. Soc.* **74**, 2118 (1952); F. Sondheimer and D. Rosenthal, *Ibid.* **80**, 3995 (1958); H. E. Zimmerman and A. Mais, *Ibid.* **81**, 3644 (1959); E. Wenkert and J. W. Chamberlin, *Ibid.* **81**, 688 (1959).
[9] A. J. Birch, H. Smith and R. E. Thornton, *J. Chem. Soc.* 1339 (1957).
[10] D. Arigoni, J. Kalvoda, H. Heusser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta* **38**, 1857 (1955).

formation of *cis*-acids from the ketone (I; R = H) is therefore not surprising, for neither route[6,7] eliminates the ambiguity of configuration at C(11).

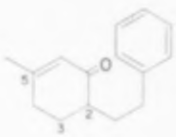
The aim of the present work was the conversion of the ketone (I; R = H) into a tricyclic acid, structurally and sterically analogous to the resin acids, by a route which should be free from this limitation. A suitable intermediate would be of the type V in which the presence of the angular methyl group would ensure formation of a *trans* ring-junction on hydrogenation.[11]

Having shown that methylation of acetylcyclohexene with methyl iodide and potassium t-butoxide gives 1-acetyl-1-methylcyclohex-2-ene, we considered it feasible to prepare the 1,1-disubstituted compound (V; R_1 = Ac, R_2 = Me) by alkylation of an unsaturated ketone (VI) which we expected to obtain *via* the ethynyl alcohol (VII) from the ketone (I; R = H). There was precedent[12] for assuming the stereostructure (V; R_1 = Ac, R_2 = Me) for the alkylation product.



VII

VIII



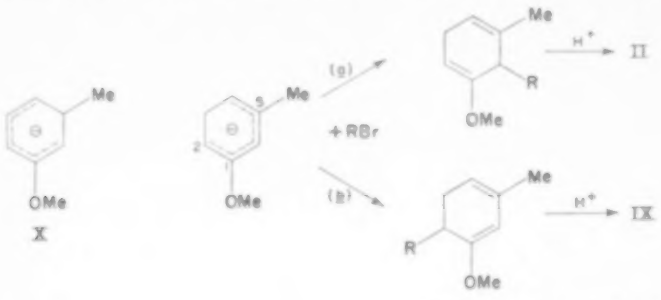
IX

Condensation of the potassium derivative of 1-methoxy-5-methylcyclohexa-1,4-diene with phenethyl bromide in liquid ammonia and subsequent acid treatment (*cf.* refs. 13 and 14) gave an oil which analysed correctly for the desired cyclohexenone (II; R = H), and from which the 2,4-dinitrophenylhydrazone of this ketone could be obtained. However, the presence of an isomeric impurity (*vide infra*) was indicated by infra-red comparison with the authentic compound (II; R = H) obtained by the method of Saha *et al.*[3,4] Cyclization of the mixture with phosphoric acid gave an oily hydrocarbon C_{15}-H_{16} (9 per cent yield based on the phenethyl bromide) and the ketone (I; R = H; 13 per cent), identical in all respects with a sample prepared from the pure cyclohexenone (II; R = H). Although the yield of the tricyclic ketone was low, this method was preferred to the published procedures[2,3,4] because of its brevity.

The oily hydrocarbon, which gave a picrate (m.p. 104·5–105·5°), is formulated as 1,2,3,4-tetrahydro-3-methylphenanthrene (VIII) on the basis of its naphthalenic absorption spectrum and its dehydrogenation to 3-methylphenanthrene (m.p. 61–62°; picrate, m.p. 137–138°).[15] The hydrocarbon was presumably formed by cyclodehydration of a 5-methyl-2-phenethylcyclohexenone (as IX): the latter thus becomes a possible structure for the isomeric impurity in the crude cyclohexenone (II; R = H) as obtained by our method. Since comparable amounts of the two compounds, II

[11] P. N. Rao and K. Raman, *Tetrahedron* **4**, 294 (1958) and refs therein cited.
[12] G. Stork and J. W. Schulenberg, *J. Amer. Chem. Soc.* **78**, 250 (1956).
[13] A. J. Birch, *J. Chem. Soc.* 1551 (1950).
[14] A. J. Birch and H. Smith, *J. Chem. Soc.* 1887 (1951).
[15] The compound was originally supposed to be 1,2,3,4-tetrahydro-1-methylphenanthrene, which might have been formed by cyclodehydration of the unsaturated ketone (II; R = H); but it was clearly shown to be different from this compound and also from the 2- and 4-methyl isomers by the melting point data which have been recorded by W. E. Bachmann and his co-workers, *J. Amer. Chem. Soc.* **62**, 2219 (1940); *J. Org. Chem.* **12**, 876 (1947); **13**, 297 (1948); **15**, 1119 (1950); *cf.* S. M. Mukherji and N. K. Bhattacharyya, *Ibid.* **17**, 1202 (1952).

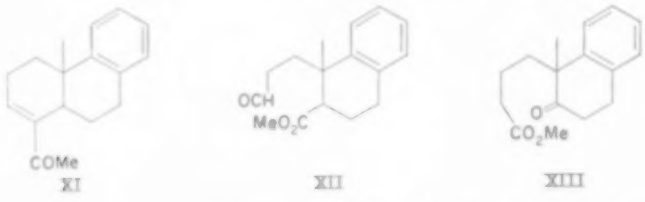
(R = H) and IX, were apparently produced in the alkylation of 1-methoxy-5-methylcyclohexa-1,4-diene, it is supposed that the dienate anion is susceptible to electrophilic attack at C(6) and C(2) at comparable rates (Paths *a* and *b* below). A possible



alternative to Path *b* is the prototropic tautomerism[13] of the dienate anion to the anion (X), which should give rise by alkylation and subsequent hydrolysis to the Δ^2-isomer of IX. This explanation may be preferred, since it is normally the *central* carbon atom which suffers electrophilic attack in such mesomeric dienate systems.[13]

The ketone (I; R = H) is extremely unreactive; and treatment with lithium acetylide in liquid ammonia under very vigorous conditions[16] gave the ethynyl alcohol (VII) in only 40 per cent yield. Several other ethynylation techniques, which are described in the Experimental Section, were found to be even less satisfactory.

When treated with boiling formic acid, the ethynyl alcohol was converted in 50 per cent yield into an $\alpha\beta$-unsaturated ketone which had ν 1670 and 1355 cm^{-1} ($CH_3{\cdot}CO{\cdot}C{=}C$). This was shown to be an isomer (XI) of the required compound (VI) by its ultra-violet absorption maximum at 234 mμ (log ε 3·94) (*cf.* acetylcyclohexene[17] which has λ_{max} 232 mμ, log ε 4·10): one would predict λ_{max} 254 mμ for the ketone (VI). The possibility that the product actually had the structure VI, and that the conjugated carbonyl band was shifted by as much as 20 mμ by overlap with the aromatic K-band at 216 mμ (log ε 4·03) was intrinsically unlikely, and could be discounted because a subtraction curve of the ultra-violet spectrum of the saturated ketone (I; R = H) from

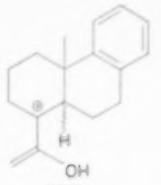


that of our product had λ_{max} 235 mμ (log $\Delta\varepsilon$ 3·93). Finally, chemical proof of the position of the ethylenic bond was obtained by Castells and Meakins' degradative procedure.[18] Treatment with osmium tetroxide followed by lithium aluminium hydride gave a hydroxylated product which underwent fission with lead tetraacetate to give an aldehydo-acid. Both the aldehydo-acid and the corresponding methyl ester (XII),

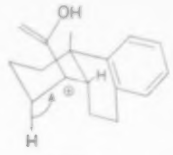
[16] *cf.* P. A. Robins and J. Walker, *J. Chem. Soc.* 3249 (1956).
[17] A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy* (2nd Ed) p. 278. Arnold, London (1957).
[18] J. Castells, Ph.D. Thesis, Manchester University (1955); J. Castells and G. D. Meakins, *Chem. & Ind.* 248 (1956).

ν 2857 (aldehydic CH) and 1739 cm^{-1} (aldehydic and ester C=O groups), gave positive Schiff tests. The isomeric ketone (VI) would have been converted into a *keto*-ester (XIII) by this sequence of reactions.

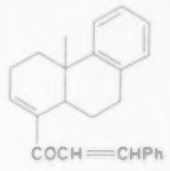
The formation from the ethynyl alcohol of the $\Delta^{1(2)}$-ketone (XI) rather than the isomer (VI) with the tetrasubstituted ethylenic bond has not been satisfactorily explained. It may imply that the angular hydrogen atom is unfavourably disposed for elimination from some cationic intermediate in the rearrangement, such as XIV,[19] i.e.



XIV



XIV A

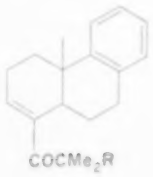


XV

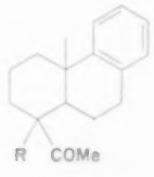
that the C(11)—H bond and the trigonal, positive centre of XIV are very nearly coplanar. This situation is possible only if the intermediate (XIV) is *cis*-fused and in the conformation XIV A. The axial hydrogen atom at C(2) would then be preferentially eliminated as a proton. The further implication would be that the AB-ring-fusion is *cis* in both the unsaturated ketone (XI) and its acetylenic precursor (VII).

In spite of the failure of the projected stereospecific synthesis at this stage, it was of interest to study the alkylation of the ketone (XI). With methyl iodide and either sodium t-amylate in benzene or potassium t-butoxide in t-butanol, no 1,1-disubstituted compound was obtained, the sole product being an $\alpha\beta$-unsaturated ketone (λ_{max} 229 mμ, ν 1674 cm^{-1}). Methylation had evidently occurred at the methyl group rather than C(1); for the infra-red band of the parent (XI) at 1355 cm^{-1} (CH_3 adjacent to C=O) had disappeared, and the compound did not react with benzaldehyde under conditions which converted XI into its benzylidene derivative (XV). These observations, together with the elementary analysis, indicate that the substance is either the t-butyl (XVI; R = Me) or the isopropyl (XVI; R = H) ketone.

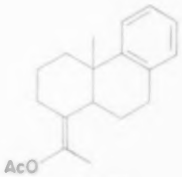
The Favorskii rearrangement has potential uses in diterpenoid synthesis as a method of introducing *gem*-groupings,[20,21] and the following reactions, which were also expected to establish the stereochemistry of the unsaturated ketone (XI), are illustrative.



XVI



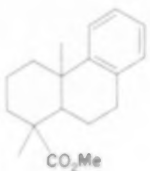
XVII



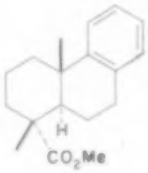
XVIII

[19] M. S. Newman, *J. Amer. Chem. Soc.* **75**, 4740 (1953); *cf.* M. F. Ansell, J. W. Hancock and W. J. Hickinbottom, *J. Chem. Soc.* 911 (1956).
[20] Since the appearance of our preliminary communication, *Chem. & Ind.* 1450 (1959), G. Stork and I. J. Borowitz, *J. Amer. Chem. Soc.* **82**, 4307 (1960), have drawn further attention to applications of this type.
[21] For a steroidal example see N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron* **3**, 144 (1958).

Reduction of the unsaturated ketone (XI) with sodium in liquid ammonia followed by reoxidation of some hydroxylic material gave the saturated ketone (XVII; R = H) in 82 per cent yield. The corresponding enol acetate (XVIII) was obtained by treatment with acetic anhydride and toluene-*p*-suiphonic acid, and converted into the bromo-ketone (XVII; R = Br) by reaction with hypobromous acid. The enol acetate and the bromo-ketone were not purified, since their infra-red spectra provided adequate confirmation of the structures assigned to them. The bromo-ketone underwent the Favorskii rearrangement when heated with methanolic sodium methoxide (*cf.* ref. 21) to give a mixture of methyl esters (ca. 45 per cent). By-products were the ketone (XVII; R = H) (ca. 10 per cent), which must have been present in the crude bromo-ketone, and some hydroxy-ketonic material. Rechromatography of the mixture of esters gave semi-solid fractions, from which a compound $C_{18}H_{24}O_2$, m.p. 114–115°, was isolated in very low yield by recrystallization from light petroleum.



XIX



XX

At this time, only three of the four possible racemic esters (XIX) had been described,[6,22] the unknown stereoisomer being methyl (±)-desisopropyldehydroabietate (XX). The melting point of our product showed that it was not identical with any of the known esters. In order to compare it with the known (±)-desisopropyldehydroabietic acid,[7] we hydrolysed the ester, but were unable to obtain a crystalline acid because of contamination of the material with oxidation products of the solvent (ethylene glycol). However, a minute sample of Ghatak's desisopropyldehydroabietic acid, m.p. 174–175°, was successfully converted into a methyl ester by the use of diazomethane. After sublimation, this had m.p. 115° undepressed by admixture with the Favorskii product.[23]

Since the *trans*-ester (XX) was obtained from the bromo-ketone only in very low yield (ca. 3 per cent) and since much uncrystallizable material was concomitantly produced, it is unjustifiable to conclude that the unsaturated ketone (XI) has a *trans* ring-junction. It need only have contained a very small proportion of the 11α-isomer, or even of the compound VI, the presence of which in trace quantity would not have been revealed by ultra-violet spectroscopy. In the latter case, sodium-ammonia reduction would presumably have given at least some 11α-material. The possible persistence of traces of isomeric impurity through several steps is understandable in view of the fact that, with the exception of the final product, all the compounds encountered in this work were oils.

[22] Ref. 7 and refs therein cited.
[23] Methyl (±)-desisopropyldehydroabietate has very recently been synthesized by a different route by E. Wenkert and A. Tahara, *J. Amer. Chem. Soc.* **82**, 3229 (1960).

EXPERIMENTAL*

1-Acetyl-1-methylcyclohex-2-ene

A solution of 1-acetylcyclohexene (10 g) and potassium t-butoxide (from 9·6 g metal) in dry t-butanol (250 ml) was stirred and warmed gently under nitrogen for 15 min. With constant stirring and passage of nitrogen, the solution was treated dropwise with methyl iodide (70 g) at 0°, and then kept at room temp for 2½ hr. The precipitated potassium iodide was collected, and its aqueous solution extracted with ether. The dried ethereal extract was combined with the filtered reaction mixture and distilled to give *1-acetyl-1-methylcyclohex-2-ene* (3·7 g), b.p. 58–67°/10 mm, n_D^{16} 1·4668. (Found: C, 77·8; H, 10·3. $C_9H_{14}O$ requires: C, 78·2; H, 10·2%). The *semicarbazone*, recrystallized twice from methanol, had m.p. 136°. (Found: C, 61·4; H, 8·7; N, 21·6. $C_{10}H_{17}ON_3$ requires: C, 61·5; H, 8·8; N, 21·5%).

3-Methyl-2-phenethylcyclohex-2-enone (II; R = H)

The ketone was obtained by Stork and Burgstahler's method[2] as a pale yellow oil, b.p. 118–120°/0·1 mm. (Found: C, 84·3; H, 8·5. Calc. for $C_{15}H_{18}O$: C, 84·1; H, 8·4%). Prepared by the method, of Saha *et al.*,[3,4] it had b.p. 110–117°/0·1 mm, n_D^{16} 1·5525. (Found: C, 84·4; H, 8·5%) and slowly solidified at room temp. The 2,4-dinitrophenylhydrazone had m.p. 172° (lit.,[4] 172°), the semicarbazone m.p. 183–184° (lit.,[2] 185°).

1,2,3,4,9,10,11,12-Octahydro-12-methyl-1-oxophenanthrene (I; R = H)

(A) Obtained from the preceding compound by treatment with phosphoric acid at 150–155° (ref. 4), the ketone had, after two distillations, b.p. 115–120°/0·7 mm, n_D^{18} 1·5643, λ_{max} 266, 273, inflexion at 290 mμ (log ε 2·69, 2·64, 1·74, respectively). (Found: C, 84·4; H, 8·7. Calc. for $C_{15}H_{18}O$: C, 84·1; H, 8·5%). The semicarbazone had m.p. 225–227° (lit.,[2] 227–228°).

(B) A solution of 1-methoxy-5-methylcyclohexa-1,4-diene[24] (100 g) and potassium amide (from 44 g metal) in liquid ammonia (2·5 l.) was stirred for 20 min, and then treated dropwise over 2 hr with phenethyl bromide (100 g) in dry ether (200 ml). The mixture was stirred for 2 hr, then treated with ammonium chloride (100 g), followed by water (2·5 l.). Isolation with ether gave an oil which was heated under reflux with 2 N sulphuric acid (200 ml) for 2 hr. The product was extracted with ether, washed with 10% sodium carbonate solution and then with water, dried and distilled. The fraction of b.p. 102–112°/0·05 mm gave, on redistillation, an oil (54 g), b.p. 124–130°/0·3 mm, n_D^{17} 1·5512. (Found: C, 83·8; H, 8·3%). There were significant differences between the infra-red spectrum of this product and that of 3-methyl-2-phenethylcyclohex-2-enone (II; R = H). However, when treated with Brady's reagent, the product gave the 2,4-dinitrophenylhydrazone (m.p. and mixed m.p. 172°) of the latter ketone.

The oil (53 g) was treated with phosphoric acid under the conditions used in (A) above, and then twice distilled at 0·05 mm to give an oil (31 g), n_D^{18} 1·5860. Its infra-red spectrum showed all the bands which were present in the spectrum of authentic octahydro-12-methyl-1-oxophenanthrene, and several additional bands due to impurities. Chromatography of a portion (960 mg) on alumina (60 g) and elution with light petroleum (350 ml) gave fraction 1 (360 mg) which was non-ketonic. Elution with 1:1 light petroleum–benzene (200 ml) gave the tricyclic ketone (I; R = H; 480 mg), the infra-red spectrum of which was identical with that of the authentic ketone. The semicarbazone prepared from this specimen had m.p. 225–227°. Further elution with the same solvent (150 ml) gave an unidentified saturated ketone (60 mg), which was unaffected by treatment with ethanolic sodium ethoxide.

Fraction 1 (2·03 g), from a similar chromatogram, was rechromatographed on alumina (100 g). Elution with light petroleum (b.p. 40–60°; 200 ml) gave, after distillation, *1,2,3,4,-tetrahydro-3-methylphenanthrene* (VIII; 1·64 g) as an oil, b.p. 155° (bath)/13 mm, n_D^{19} 1·6110, ν 815, 792, 767, 745 cm^{-1}, λ_{max} 229, 274·5, 280, 291, 307·5, 314, 321·5 mμ (log ε 4·99, 3·74, 3·77, 3·67, 3·03, 2·82, 2·96, respectively). (Found: C, 91·9; H, 8·1. $C_{15}H_{16}$ requires: C, 91·8; H, 8·2%). The *picrate*, orange-yellow needles from ethanol, had m.p. 104·5–105·5°. (Found: C, 59·1; H, 4·3; N, 9·5. $C_{21}H_{19}O_7N_3$

* Ultra-violet spectra were measured for ethanol solutions, infra-red spectra for liquid films. Melting points were taken on a Kofler block. For chromatography, Peter Spence's "Grade H" alumina was used; deactivated alumina contained 5% of 10% aqueous acetic acid. Unless otherwise stated, "light petroleum" refers to the fraction of b.p. 60–80°.

[24] A. J. Birch, *J. Chem. Soc.* 593 (1946).

requires: C, 59·3; H, 4·5; N, 9·9%). Further elution with light petroleum (100 ml) gave an intermediate fraction (198 mg) and then (with 300 ml solvent) *3-methyl-2-phenethylanisole* (198 mg), b.p. 153° (bath)/13 mm, n_D^{15} 1·5636, ν 1255 (s), 1034 (m), 803 (m), 772 (m), 696 (s) cm^{-1}, λ_{max} 275, 280 mμ (log ε 3·41, 3·40 respectively). (Found: C, 84·7; H, 7·9. $C_{16}H_{18}O$ requires: C, 84·9; H, 8·0%).

The tricyclic ketone (I; R = H) obtained by this method (B) was not in general purified chromatographically, since its contaminants were easily removed during the purification of the ethynylation product (VII).

Dehydrogenation of the tetrahydromethylphenanthrene (VIII)

The above hydrocarbon (1 g) was heated under nitrogen with 5% palladized charcoal at 300° for 1 hr. Chromatography on alumina (50 g) and elution with light petroleum (b.p. 40–60°; 100 ml) gave a mixed fraction (126 mg) containing much starting material; further elution with this solvent (150 ml) gave 3-methylphenanthrene (736 mg), which, after three recrystallizations from ethanol, had m.p. 57·5–60° (lit.,[23] 62–63°), λ_{max} 252, 276·5, 284, 295·5, 317·5, 324·5, 332, 340, 347·5 mμ (log ε 4·91, 4·19, 4·06, 4·17, 2·57, 2·52, 2·75, 2·54, 2·81, respectively). The picrate, orange yellow needles from ethanol, had m.p. 137–138° (lit.,[23] 137–138°). (Found: C, 60·2; H, 3·6; N, 10·2. Calc. for $C_{21}H_{15}O_7N_3$: C, 59·9; H, 3·6; N, 10·0%). The picrate was dissolved in benzene and adsorbed on an alumina column. Benzene eluted 3-methylphenanthrene, which was obtained as needles, m.p. 61–62°, after two recrystallizations from ethanol.

1-*Ethynyl*-1,2,3,4,9,10,11,12-*octahydro*-1-*hydroxy*-12-*methylphenanthrene* (VII)

(A) Lithium (4·2 g) was dissolved in liquid ammonia (500 ml) through which a rapid stream of dry, acetone-free acetylene was being passed, and the solution was placed in a cooled steel bomb (capacity ca. 1 l.) together with the crude tricyclic ketone (I; R = H; 8·5 g) in dry tetrahydrofuran (200 ml). The mixture was saturated with acetylene at −60° (ca 1 hr); then the bomb was sealed and shaken at room temp for 46 hr. After being cooled to −60°, the bomb was opened and its contents were treated with brine and ether. The oily product (6·9 g), which was isolated with ether, was chromatographed on deactivated alumina (500 g). Elution with 9:1 light petroleum–benzene (1·5 l.) gave non-ketonic material (2·85 g) (the impurities in the starting material); further elution with the same solvent mixture (2 l.) gave the pure ketone (I; R = H; 0·58 g), and then (with 0·5 l. solvent) a mixed fraction (0·09 g). Elution with 1:1 light petroleum–benzene (3·5 l.) gave the *ethynyl alcohol* (VII; 1·90 g) as a viscous oil, ν 3521 and 3430 (OH), and 3295 cm^{-1} (≡CH). (Found: C, 84·6; H, 8·5. $C_{17}H_{20}O$ requires: C, 85·0; H, 8·4%).

(B) Solutions of (i) the crude tricyclic ketone (12·3 g) in dry ether (200 ml), and (ii) potassium (50 g) in dry t-amyl alcohol (800 ml) and dry ether (250 ml) were simultaneously added dropwise over 1½ hr to dry ether (200 ml) cooled to −5° to 0°, saturated with dry, acetone-free acetylene and vigorously stirred. Passage of acetylene was continued during the addition and for a further 24 hr, during which time the solution was vigorously stirred at room temp. After the addition of brine (500 ml), the mixture was acidified with conc hydrochloric acid and extracted with ether. Evaporation of the dried organic solution gave a dark oil which was dissolved in 95% ethanol (200 ml) and treated with a 5% solution of silver nitrate in 95% ethanol (50 ml). The precipitated silver derivative, m.p. 118–122°, was washed with ethanol and ether. The filtrate and washings were poured into brine, and the oil, which was collected with ether, was treated with silver nitrate solution as before. The silver derivative (3·1 g) was heated under reflux with sodium cyanide (15 g), water (150 ml) and ethanol (10 ml) for 2½ hr. Extraction with ether gave the crude ethynyl alcohol (1·25 g), shown by its infra-red spectrum to be free from starting material.

Less vigorous ethynylating conditions (excesses of lithium acetylide in liquid ammonia or in mixtures of liquid ammonia and ether; ethynylmagnesium bromide in tetrahydrofuran) were without effect on the ketone. In an experiment using lithium acetylide in boiling ether, the silver derivative of the ethynyl alcohol was isolated in very low yield. Extensive decomposition occurred with lithium acetylide in boiling dioxan and no product could be obtained. These reactions were followed by infra-red spectroscopy, and by the testing of samples with a 5% solution of silver nitrate in 95% ethanol.

[23] R. D. Haworth, *J. Chem. Soc.* 1132 (1932).

1-*Acetyl*-3,4,9,10,11,12-*hexahydro*-12-*methylphenanthrene* (XI)

The ethynyl alcohol (VII; 1·71 g) was heated under reflux with 90% formic acid (50 ml) and ethanol (5 ml) for 2½ hr. The reaction mixture was poured into 10% sodium bicarbonate solution and extracted with ether. The ethereal solution was washed with bicarbonate solution, dried and evaporated. Chromatography of the viscous residue (1·66 g) on deactivated alumina (300 g) and elution with light petroleum (700 ml) gave an oil (60 mg), ν 3290 (≡CH) and 2110 cm^{-1} (C≡C); further elution (with 700 ml) gave mixed fractions (440 mg), and then (with 1400 ml) the *unsaturated ketone* (XI; 637 mg) as a viscous oil, b.p. 108–111° (bath)/0·04 mm, n_D^{17} 1·5740, λ_{max} 216, 234 mμ (log ε 4·03, 3·94 respectively). (Found: C, 85·1; H, 8·3. $C_{17}H_{20}O$ requires: C, 85·0; H, 8·4%). The orange-yellow 2,4-*dinitrophenylhydrazone*, recrystallized twice from ethanol–ethyl acetate, had m.p. 209–213°. (Found: C, 65·2; H, 5·9. $C_{23}H_{24}O_4N_4$ requires: C, 65·7; H, 5·8%). Rechromatography of the mixed fractions (440 mg) gave an unidentified oil (74 mg), ν 1717 cm^{-1}, and the acetylhexahydromethylphenanthrene (250 mg).

The ketone was obtained in 8% yield when phosphoric oxide in benzene was used to effect the rearrangement.

Oxidative degradation of the unsaturated ketone (XI)

A solution of the ketone (XI; 23 mg) and osmium tetroxide (ca. 35 mg) in dry ether (3 ml) and dry pyridine (0·1 ml) was boiled for 1 hr, and then left overnight at room temp. The reagents were removed at 100° *in vacuo*, and the residue was heated under reflux with pure tetrahydrofuran (5 ml) and lithium aluminium hydride (ca. 200 mg) for ½ hr. The excess of lithium aluminium hydride was decomposed with ethyl acetate, and water was added. The viscous product (24 mg), which was isolated with chloroform, had ν 3390 (OH) and 1709 cm^{-1} (w) (satd ketone).

A solution of the hydroxylated material and lead tetra-acetate (100 mg) in acetic acid (4 ml) was set aside at room temp for 12 hr, then evaporated at 100°/0·05 mm. After the addition of water, the product (29 mg) was isolated with ether. The infra-red spectrum indicated the presence of CO_2H and CHO. A portion (10 mg), dissolved in pure dioxan (0·5 ml), gave a positive Schiff test.

The remainder (19 mg) in dry ether (1·5 ml) was esterified with ethereal diazomethane, then chromatographed on deactivated alumina (3 g). Elution with ether (15 ml) gave the ester (XII) as a viscous oil (12 mg): ν 2857 (aldehydic CH) and 1739 cm^{-1} (aldehydic and ester C=O groups): Schiff test positive.

Simultaneously with the Schiff tests carried out in this experiment, blank tests were done on the dioxan used as solvent: these gave only very faint pink colorations after standing for several minutes.

Condensation of the ketone (XI) *with benzaldehyde*

The ketone (XI; 190 mg) was heated under reflux in ethanol (2 ml) with benzaldehyde (0·08 ml) and potassium hydroxide (25 mg) for ½ hr. The dark solution was diluted with water, acidified with dil hydrochloric acid and extracted with ether. The ethereal solution was washed with saturated sodium bisulphite solution and then with water, dried and evaporated. Chromatography of the residue on deactivated alumina (25 g) and elution of the yellow band with 4:1 light petroleum–benzene (135 ml) gave 1-*cinnamoyl*-3,4,9,10,11,12-*hexahydro*-12-*methylphenanthrene* (XV; 112 mg) as a yellow glass which, after drying at 80° *in vacuo*, had λ_{max} 227, 297 mμ (log ε 4·03, 4·20 respectively). (Found: C, 87·7; H, 7·4. $C_{24}H_{24}O$ requires: C, 87·8; H, 7·4%).

Methylation of the unsaturated ketone (XI)

A mixture of the ketone (XI; 320 mg), methyl iodide (8 ml) and 16 ml of a 0·8 M solution of sodium t-amylate in benzene was set aside under nitrogen at room temp for 1½ hr. After dilution with water and acidification, the product was isolated with ether and chromatographed on deactivated alumina (20 g). Elution with 9:1 light petroleum–benzene (80 ml) gave an *α/β-unsaturated ketone* (140 mg) which, after distillation, was obtained as a pale yellow oil, b.p. 115° (bath)/0·05 mm, λ_{max} 229 mμ ($E_{1cm}^{1\%}$ 209), ν 1674 cm^{-1}. (Found: C, 85·2; H, 9·1. $C_{19}H_{24}O$ requires: C, 85·0; H, 9·0. $C_{20}H_{26}O$ requires: C, 85·1; H, 9·3%). Attempts to prepare a 2,4-dinitrophenylhydrazone were unsuccessful.

Similar results were obtained by the use of potassium t-butoxide in t-butanol as basic reagent.

The ketone was unaffected (almost quantitative recovery) by treatment with benzaldehyde and

ethanolic potassium hydroxide under the conditions used for the preparation of the benzylidene derivative (XV).

1-*Acetyl*-1,2,3,4,9,10,11,12-*octahydro*-12-*methylphenanthrene* (XVII; R = H)

Sodium (110 mg, 3 g atoms) was added with swirling to a solution of the unsaturated ketone (XI; 368 mg) in dry ether (10 ml) and liquid ammonia (25 ml). After 15 min, the solution was treated with sufficient ammonium chloride to destroy the blue colour. After the addition of water, extraction with ether gave an oil (368 mg), ν 3448 (OH) and 1700 cm^{-1} (satd ketone), which was dissolved in acetic acid (2 ml) and treated with 5·2 ml of a 2% solution of chromium trioxide in acetic acid. After 1 hr at room temp, the product (340 mg) was isolated by dilution with water and extraction with ether, and chromatographed on alumina (30 g). Elution with 1:1 light petroleum–benzene (400 ml) gave the *saturated ketone* (XVII; R = H; 305 mg) as an oil. A portion distilled for analysis had b.p. 107° (bath)/0·15 mm. (Found: C, 84·3; H, 9·2. $C_{17}H_{22}O$ requires: C, 83·9; H, 9·2%).

The enol acetate (XVIII) (*cf.* ref. 26)

A solution of the ketone (XVII; R=H; 240 mg) and toluene-*p*-sulphonic acid (600 mg) in redistilled acetic anhydride (20 ml) was slowly distilled. After 1 hr, fresh acetic anhydride (10 ml) was added to replace that which had been distilled out of the mixture. Similar replacements with fresh acetic anhydride were made at intervals over a further 1½ hr. At the end of this period, the anhydride was removed by distillation, finally at 100°/12 mm. The residue was dissolved in ether, and the solution was washed with ice-cold 5% sodium hydroxide solution and then with water, dried and evaporated to give the enol acetate (290 mg) as a dark brown oil, ν 1750 and 1208 cm^{-1} (enol acetate):

no infra-red bands due to ketone or $\diagdown C{=}CH_2$.

Attempts to prepare the compound using acetic anhydride and perchloric acid in carbon tetrachloride solution[27] failed.

1-*Acetyl*-1-*bromo*-1,2,3,4,9,10,11,12-*octahydro*-12-*methylphenanthrene* (XVII; R = Br) (*cf.* ref. 28)

Solutions of (i) the crude enol acetate (XVIII; 332 mg) in dry t-butanol (10 ml), and (ii) N-bromosuccinimide (220 mg, 1·05 mol) in t-butanol (20 ml) and N sulphuric acid (11 ml) were mixed and set aside in the dark for 3 hr at room temp. The solution was treated with saturated sodium bisulphite solution, diluted greatly with water and extracted with ether. The ethereal solution was washed with 5% sodium hydroxide solution and then with water, dried and evaporated to give the crude bromoketone (XVII; R = Br; 300 mg) as a dark brown oil, ν 1700 and 1351 cm^{-1} (methyl ketone): positive Beilstein test (Br).

Favorskii rearrangement of the bromo-ketone (XVII; R = Br)

The bromo-ketone (300 mg) was heated under reflux for 6 hr with a solution of sodium methoxide (from 1 g sodium metal) in dry methanol (30 ml). After removal of most of the methanol by distillation, water and ether were added, and the organic material was separated into neutral (195 mg) and acidic (49 mg) fractions by the usual acid-alkali treatment. The acidic material was esterified with diazomethane to give a second neutral fraction. The combined neutral products (238 mg), which gave a faint Beilstein test, were chromatographed on deactivated alumina (50 g). Light petroleum (350 ml) eluted oils (98 mg), ν 1727 and 1245 cm^{-1} (carboxylic ester); 19:1 light petroleum–benzene (100 ml) gave a mixed fraction (10 mg) which was combined with the earlier fractions for rechromatography. Further elution with the same solvent mixture (150 ml) gave the ketone (XVII; R = H; 29 mg). Stronger solvents eluted oily material (33 mg) which was shown by its infra-red spectrum to contain OH and C=O.

[26] C. W. Marshall, T. H. Kritchevsky, S. Liebermann and T. F. Gallagher, *J. Amer. Chem. Soc.* **70**, 1837 (1948).
[27] D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones and T. Walker, *J. Chem. Soc.* 747 (1954).
[28] H. V. Anderson, E. R. Garrett, F. H. Lincoln, A. H. Nathan and J. A. Hogg, *J. Amer. Chem. Soc.* **76**, 743 (1954); B. J. Magerlein, D. A. Lyttle and R. H. Levin, *J. Org. Chem.* **20**, 1709 (1955).

The ester-containing fractions (108 mg) from the previous chromatogram were rechromatographed on "Grade H" alumina (10 g). Elution with 4:1 light petroleum–benzene (170 ml) gave an oil (52 mg) which solidified slowly; then 1:2 light petroleum–benzene (30 ml) eluted more acetyloctahydromethylphenanthrene (5 mg). The semisolid product gave plates (9 mg), m.p. 113–115°, after two recrystallizations from light petroleum (b.p. 40–60°). After filtration in light petroleum solution through charcoal and a third recrystallization from the same solvent, *methyl (±)-desisopropyldehydroabietate* (XX; 6·3 mg) was obtained as plates, m.p. 114–115°. (Found: C, 79·1; H, 8·7. $C_{21}H_{24}O_2$ requires: C, 79·4; H, 8·9%). The m.p. was undepressed by admixture with an authentic sample of the ester (m.p. 115°) prepared from (±)-desisopropyldehydroabietic acid (*vide infra*).

Correlation of the ester (XX) *with Ghatak's (±)-desisopropyldehydroabietic acid*[7]

(A) The ester (4·0 mg) was heated under reflux for 5 hr with 5 ml of a solution of potassium hydroxide (5 g) in water (3 ml) and ethylene glycol (15 ml), which had previously been boiled until the temp of the liquid reached 150°. Dilution with water, addition of ether, and the usual acid-alkali treatment gave neutral (6·1 mg) and acidic (9·3 mg) fractions. Both fractions must have been contaminated with glycol oxidation products, as crystalline material could be isolated from neither.

(B) Ghatak's (±)-desisopropyldehydroabietic acid (0·25 mg), m.p. 174–175°, in pure tetrahydrofuran (0·1 ml) was esterified with an excess of ethereal diazomethane. Removal of the solvents and reagent *in vacuo* at room temp gave an oil which solidified when scratched (m.p. 100–105°, traces to 115°). Recrystallization of the minute amount of the ester so obtained was impossible, but after sublimation at 93°/0·05 mm, it melted sharply at 115°. The m.p. was undepressed by admixture with methyl (±)-desisopropyldehydroabietate (m.p. 114–115°) prepared by the Favorskii rearrangement.

Acknowledgements—We are grateful to Drs. P. C. Dutta and U. R. Ghatak for a sample of (±)-desisopropyldehydroabietic acid. One of us (A. C. D.) thanks the Department of Scientific and Industrial Research for a Maintenance Allowance, and the Principal and Fellows of Brasenose College, Oxford, for the award of a Senior Hulme Scholarship.

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A SIMPLE SYNTHESIS OF "QUEEN SUBSTANCE"*

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Abstract—A convenient synthesis of *trans*-9-oxodec-2-enoic acid is described.

IN December 1959 Butler, Callow and Johnston[1] published data which indicated that "queen substance"—a physiologically highly active material secreted in the mandibular glands of the queen honeybees, which inhibits the development of ovaries in the worker bees and prevents the construction of queen cells[2,3]—was structurally closely related to *trans*-10-hydroxydec-2-enoic acid (royal jelly acid) (I).[4,5] Interpretation of the reproduced infra-red spectrum[1] led us to the conclusion that the substance was either the aldehydo-acid 10-oxodec-2-enoic acid (II) or the isomeric keto-acid (III), of which, on biogenetic grounds, the structure II seemed somewhat the more probable.

$HO(CH_2)_7{\cdot}CH{=}CH{\cdot}COOH$ (I) $\quad OCH{\cdot}(CH_2)_7{\cdot}CH{=}CH{\cdot}COOH$ (II) $\quad OCH{\cdot}(CH_2)_8\ldots.$

$CH_3CO{\cdot}(CH_2)_5{\cdot}CH{=}CH{\cdot}COOH$ (III)

Since we had recently synthesized royal jelly acid,[5] we examined several schemes for the preparation of both compounds (II) and (III).

While this work was in progress Callow and Johnston[6] showed that "queen substance" was, in fact, identical with the keto-acid (III), which they synthesised from azelaic acid in nine steps. At about the same time Barbier and Lederer[7] reached the same conclusion as a result of their investigations of the natural product.

The present communication describes a much simpler synthesis of *trans*-9-oxodec-2-enoic acid (III) from the known 7-oxo-octanoic acid (IVa),[8] which is readily accessible from cyclohexanone and acetic anhydride by way of 2-acetylcyclohexanone.[8,9] The acid (IVa) was converted in excellent yield into the corresponding acid chloride (IVb) by means of oxalyl chloride; thionyl chloride proved a less satisfactory reagent for this purpose. Reduction of 7-oxo-octanoyl chloride (IVb) according to Rosenmund gave 7-oxo-octanal (V) which, after purification, was condensed with malonic acid under the conditions of the Doebner reaction. Crystallization of the resulting product from ether–light petroleum (b.p. 40–60°) furnished the keto-acid (III) as transparent,

* U.K. Patent Application No. 33,447/60 (September, 1960).

[1] C. G. Butler, R. K. Callow and N. C. Johnston, *Nature, Lond.* **184,** 1871 (1959).
[2] C. G. Butler, *Bee World* **40,** 269 (1959).
[3] M. Barbier and J. Pain, *C. R. Acad. Sci., Paris* **250,** 3740 (1960).
[4] A. Butenandt and H. Rembold, *Z. Physiol. Chem.* **308,** 284 (1957).
[5] G. I. Fray, R. H. Jaeger and Sir Robert Robinson, *Tetrahedron Letters* No. 4, 15 (1960).
[6] R. K. Callow and N. C. Johnston, *Bee World* **41,** 152 (1960).
[7] M. Barbier and E. Lederer, *C.R. Acad. Sci., Paris* **250,** 4467 (1960).
[8] R. C. Hauser and J. T. Adams, *J. Amer. Chem. Soc.* **66,** 345 (1944).
[9] H. Meerwein and D. Vossen, *J. Prakt. Chem.* **141,** 149 (1934).

elongated plates, m.p. 53–54°, raised by re-crystallization from the same solvent mixture to 54·5–55·5° (constant). Callow and Johnston[6] quote m.p. 45–52° for their synthetic product and m.p. 52–53·5° for the purified material from natural sources.

$CH_3CO{\cdot}(CH_2)_5COR$ $CH_2CO{\cdot}(CH_2)_5CHO$

IVa, R=OH V

IVb, R=Cl

The acid (III) prepared in the above manner gave a positive iodoform test and its infra-red spectrum was consistent with the structure of "queen substance"; it formed a yellow 2,4-dinitrophenylhydrazone, m.p. 127–128°. The assignment of the *trans*-configuration follows from the mode of synthesis.[10]

After this work was completed we learnt that Barbier *et al.*[11] had obtained the keto-acid (III), m.p. 51–54° by an elegant synthesis, starting from cycloheptanone.

EXPERIMENTAL

Trans-9-*Oxodec*-2-*enoic acid* (III). Oxalyl chloride (22 g) was added dropwise to a solution of 7-oxo-octanoic acid[8] (9·4 g) in dry benzene (20 cc) at 0° under nitrogen. After the addition was complete the mixture was allowed to react at room temperature for 45 min and finally at 60–70° for 1 hr. Excess of reagent and solvent were removed under reduced pressure and the residue was fractionated; the acid chloride (IVb) distilled as a colourless liquid, b.p. 90–92°/0·25 mm (9·15 g = 87% yield). Its infra-red spectrum had strong bands at 5·51 (COCl) and 5·81 μ (C=O). An experiment carried out under similar conditions, using thionyl chloride as the reagent, gave the acid chloride in only 48% yield, leaving a large amount of charred material as residue after distillation. The above acid chloride (9·1 g), dry xylene (120 cc) and palladium on barium sulphate (1·2 g of 5%) were heated in an oil bath at 150–160° while a vigorous stream of hydrogen was passed through the stirred mixture. Evolution of hydrogen chloride virtually ceased after 45 min; the reaction mixture was rapidly chilled, a little Celite added, and the solids removed by filtration. After removal of the solvent under reduced pressure and fractionation of the residue, 7-oxo-octanal (V) was obtained as a colourless, fragrant liquid, b.p. 62–64°/0·2 mm (4·1 g). The infra-red spectrum showed peaks at 3·65 (aldehydic C—H) and 5·79 μ (comprising aldehydic and ketonic C=O). The keto-aldehyde gave persistently low values for carbon content, doubtless due to absorption of oxygen from the air.

Solutions of 7-oxo-octanal (4·1 g) and of malonic acid (3·3 g) in dry pyridine (13 cc each) were mixed at 0° and piperidine (12 drops) was added. The mixture was kept in the dark at 50° for 48 hr chilled and slowly added to ice-cold 50% sulphuric acid (60 cc). The product was extracted with ether, the extract washed twice with dilute hydrochloric acid and then with saline, and dried. After removal of the solvent the crude residue solidified; crystallisation from ether–light petroleum (b.p. 40–60°) gave *trans*-9-oxodec-2-enoic acid as large, transparent colourless plates, m.p. 53–54° (2·51 g). Recrystallisation of a sample from the same solvent mixture raised the m.p. to 54·5–55·5°, unchanged on further crystallization. The infra-red spectrum (Nujol mull) had bands at 5·83 (C=O), 5·90 (conjugated C=O), and 6·07 μ (conjugated C=C). (Found: C, 65·3; H, 8·9. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·7%).

The 2,4-*dinitrophenylhydrazone* of the keto-acid (III) was prepared with Brady's reagent and crystallized from ethanol as yellow prisms, m.p. 127–128° (Found: C, 53·1; H, 5·9; N, 15·2. $C_{16}H_{20}O_6N_4$ requires C, 52·8; H, 5·5; N, 15·4%).

[10] K. V. Auwers *Ann.* **432**, 46 (1923).

[11] M. Barbier, E. Lederer and T. Nomura, *C. R. Acad. Sci., Paris* **251**, 1133 (1960).

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SYNTHESIS OF OXYAVICINE

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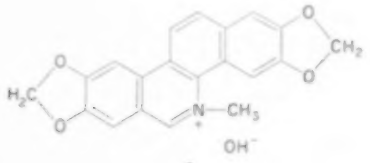
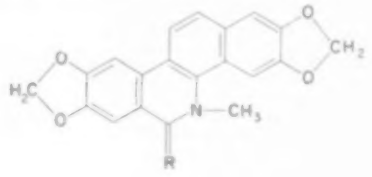
(*Received* 6 *March* 1961)

Abstract—The structure (I) assigned to the alkaloid avicine has been confirmed by a synthesis of oxyavicine (III).

ARTHUR *et al.*[1] isolated from the root bark of *Zanthoxylum avicennae* an alkaloid avicine, to which they assigned structure I. The alkaloid is isomeric with sanguinarine and was found to disproportionate to a mixture of dihydroavicine (II) and oxyavicine (III). The structure of avicine has now been confirmed by synthesis of oxyavicine along the Robinson–Bailey route starting from the tetralone (VIII) which had been prepared earlier in this laboratory[2] in connexion with other work.



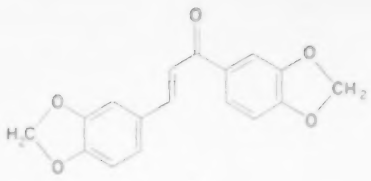
I



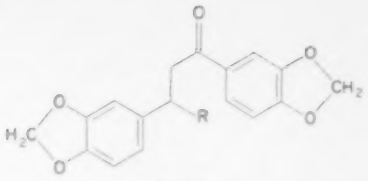
II: R = H_2
III: R = O

Condensation of acetopiperone with piperonal yielded 3,4:3′,4′-bismethylenedioxychalkone (IV). Addition of hydrogen cyanide gave the nitrile (V) which was hydrolysed to the amide (VI) with sulphuric acid. Further hydrolysis of the amide with alkali yielded the corresponding keto acid (VII). Reduction with hydrogen and palladium-charcoal in the presence of perchloric acid gave the substituted n-butyric acid which was cyclized with phosphorus oxychloride to yield 1,2,3,4-tetrahydro-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)-1-oxonaphthalene (VIII). Leuckart reaction on this afforded a separable mixture of 3,4-dihydro-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)-naphthalene and the 1-formamido derivative (IX). The former, on dehydrogenation, yielded 6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)naphthalene, identical with an authentic sample made by the method of Gopinath *et al.*[3] The formamide was cyclized with phosphorus oxychloride in toluene to 3,4,11,12-tetrahydro-6,7:2′,3′-bismethylenedioxy-1,2-benzophenanthtidine which was dehydrogenated to the benzophenanthridine (X). The methosulphate of this base, on oxidation with alkaline potassium ferricyanide, gave oxyavicine (III), identical in all respects (mixed m.p., ultra-violet and infra-red spectra) with a sample of the natural product. Oxyavicine has earlier been reduced[1] with lithium aluminium hydride to dihydroavicine.

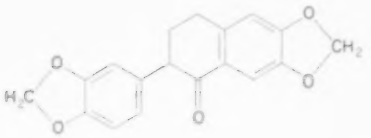
[1] H. R. Arthur, W. H. Hui and Y. L. Ng, *J. Chem. Soc.* 4007 (1959).
[2] N. Viswanathan, Ph.D. Thesis, Madras University (1959).
[3] K. W. Gopinath, T. R. Govindachari, K. Nagarajan and K. K. Purushothaman, *J. Chem. Soc.* 1144 (1957).



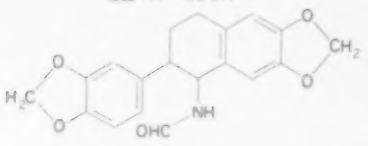
IV



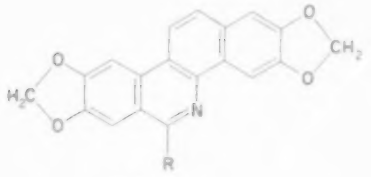
V : R = CN
VI : R = $CONH_2$
VII : R = COOH



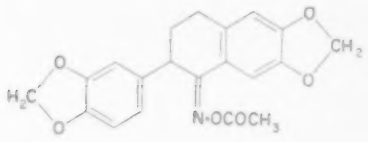
VIII



IX



X : R = H
XII : R = CH_3



XI

As in the case of other 2-aryl-1-tetralone oxime acetates investigated in this laboratory,[4] the oxime acetate (XI) made from the tetralone (VIII), on treatment with acetic acid, acetic anhydride and hydrogen chloride in a sealed tube, underwent an abnormal Schroeter reaction to furnish the substituted 9-methyl-1,2-benzophenanthridine (XII) in excellent yield.

EXPERIMENTAL

3,4:3',4'-*Bismethylenedioxychalkone* (IV). A mixture of piperonal (10 g) and acetopiperone (10·6 g) in ethanol (50 ml) was treated with aqueous NaOH (10%; 14 ml) and left overnight. The precipitated *chalkone* (17 g) was collected, washed with water and crystallized from acetone to yield yellow needles, m.p. 174° (Found: C, 68·6; H, 3·8. $C_{17}H_{12}O_5$ requires: C, 68·9; H, 4·1%).

α,γ-*Bis*(3,4-*methylenedioxyphenyl*)-γ-*oxobutyronitrile* (V). The chalkone (10 g) was dissolved in boiling 2-ethoxyethanol (70 ml) containing acetic acid (2·5 ml) and the solution transferred quickly to a water bath preheated to 100° to prevent crystallization of the chalkone. A solution of potassium cyanide (5 g) in water (9 ml) was added with stirring, during 3 min, and the heating continued for 15 min. Dilution with water gave the *nitrile* (10 g), which crystallized from ethanol as colourless needles, m.p. 141° (Found: C, 66·9; H, 4·2. $C_{18}H_{13}NO_5$ requires: C, 66·9; H, 4·0%).

α,γ-*Bis*(3,4-*methylenedioxyphenyl*)-γ-*oxobutyramide* (VI). A solution of the nitrile (6 g) in acetic acid (42 ml) was treated gradually with conc H_2SO_4 (6 ml) during 15 min. Addition of water yielded the *amide* (5·5 g) which crystallized from acetone as shining prisms, m.p. 164° (Found: C, 63·7; H, 4·4. $C_{18}H_{15}NO_6$ requires: C, 63·3; H, 4·4%).

α,γ-*Bis*(3,4-*methylenedioxyphenyl*)-γ-*oxobutyric acid* (VII). A mixture of the amide (10 g), ethanol (100 ml) and aqueous sodium hydroxide (7%; 160 ml) was refluxed for 7 hr and acidified to yield the *keto acid* (8 g). Crystallization from ethanol gave colourless needles, m.p. 169–170° (Found: C, 62·8; H, 4·4. $C_{18}H_{14}O_7$ requires: C, 63·2; H, 4·1%).

1,2,3,4-*Tetrahydro*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)-1-*oxonapathalene* (VIII). The

[4] K. W. Gopinath, T. R. Govindachari and N. Viswanathan, *Curr. Sci.* **28**, 241 (1959).

keto acid (2 g) in acetic acid (25 ml) and perchloric acid (70%; 0·5 ml) was reduced with hydrogen at a pressure of 15 lbs/in² at 60°, using palladized charcoal catalyst (5%; 0·6 g) during 2 hr. The catalyst was filtered off and the solvent removed under reduced press. Water was added and the product extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and the solvent distilled to yield α,γ-bis(3,4-methylenedioxyphenyl)butyric acid (1·8 g) as a brownish oil. This was heated at 100° for 15 min with phosphorus oxychloride (4 ml). The mixture was cooled, poured on ice and the product extracted with chloroform. The chloroform extract was washed with Na_2CO_3 solution and then with water, dried (Na_2SO_4) and the solvent removed by distillation. Chromatography of the residue in benzene over alumina yielded the *tetralone* (0·7 g) which crystallized from ethyl acetate–ethanol as needles, m.p. 170–171° (Found: C, 69·7; H, 4·6. $C_{18}H_{14}O_5$ requires: C, 69·7; H, 4·5%).

1-*Formamido*-1,2,3,4-*tetrahydro*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene* (IX). The tetralone (2 g) was heated under reflux at 180° for 3 hr with formamide (5 ml), formic acid (0·25 ml) and ammonium sulphate (0·25 g), formic acid (0·25 ml) being added every 1 hr. The mixture was cooled, diluted with water and extracted with chloroform. The dried (Na_2SO_4) chloroform extract gave, on removal of the solvent, a brownish gum which was chromatographed in benzene over alumina. The initial fractions of the eluate which had a violet fluorescence yielded, on evaporation, 3,4-*dihydro*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene* (0·2 g) which crystallized from methanol as needles, m.p. 155°, λ_{max} 225, 335 mμ (log ε 4·03, 4·04) (Found: C, 73·7; H, 5·1. $C_{18}H_{14}O_4$ requires: C, 73·5; H, 4·8%). Further elution of the column with benzene and then with benzene containing 1% ethanol gave the *formamide* (0·8 g). Crystallization from alcohol gave needles, m.p. 169–170° (Found: C, 67·6; H, 5·3. $C_{19}H_{17}NO_5$ requires: C, 67·3; H, 5·0%).

6,7-*Methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene*. A mixture of the dihydronaphthalene (0·4 g) and palladized charcoal catalyst (30%; 0·2 g) was heated at 240–250° for 10 min and the product sublimed *in vacuo* (0·2 mm). The solid sublimate, on crystallization from acetic acid, gave the *naphthalene* (0·3 g) as plates, m.p. 200°, undepressed by admixture with an authentic sample[3] (Found: C, 74·1; H, 4·0. $C_{18}H_{12}O_4$ requires: C, 74·0; H, 4·1%). The ultra-violet and infra-red absorption spectra of the two compounds were identical.

3,4,11,12-*Tetrahydro*-6,7:2′,3′-*bismethylenedioxy*-1,2-*benzophenanthridine*. The formamide (1 g) in dry toluene (10 ml) was refluxed gently for 30 min with phosphorus oxychloride (3 ml). The precipitated hydrochloride was filtered, washed with ether, and basified with ammonia, to yield the *tetrahydrobenzophenanthridine* (0·6 g). Crystallization from pyridine–ethanol gave needles, m.p. 235–236°, λ_{max} 230, 292 mμ (log ε 4·27, 3·69), λ_{infl} 315 mμ (log ε 3·61) (Found: C, 71·3; H, 4·5. $C_{19}H_{15}NO_4$ requires: C, 71·1; H, 4·7%).

6,7:2′,3′-*Bismethylenedioxy*-1,2-*benzophenanthridine* (X). The tetrahydrobenzophenanthridine (0·3 g) was heated with palladized charcoal catalyst (30%; 0·3 g) at 230–240° for 40 min in an atmosphere of nitrogen. The product was thoroughly extracted with chloroform. Removal of the solvent by distillation and crystallization of the product from pyridine gave the *benzophenanthridine* (0·15 g) as needles, m.p. 325° (decomp), λ_{max} 230, 275, 370 mμ (log ε 4·59, 4·86, 3·50), λ_{infl} 327 mμ (log ε 4·26) (Found: C, 71·5; H, 3·9. $C_{19}H_{11}NO_4$ requires: C, 71·9; H, 3·5%).

Oxyavicine (III). A solution of the above benzophenanthridine (0·1 g) in xylene (3 ml) and nitrobenzene (5 ml) was boiled for 5 min and dry methyl sulphate (0·3 ml) added to the boiling solution. A yellow precipitate rapidly appeared and after 5 min the solution was cooled and diluted with ether (15 ml). The precipitate was collected and washed with ether to yield the methosulphate (100 mg) which did not melt below 360°. A solution of the methosulphate (0·1 g) in water (30 ml) was heated on a water bath to 70° and treated dropwise with stirring with a hot solution of potassium ferricyanide (0·4 g) and potassium hydroxide (0·2 g) in water (20 ml). The mixture was stirred vigorously for 20 min at 80°, cooled and extracted with benzene. The benzene extract was washed with dil HCl, then with water and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue in chloroform over alumina yielded *oxyavicine* (20 mg) as needles from ethanol, m.p. 276–277°, undepressed by admixture with a sample of the natural product. The ultra-violet and infra-red spectra of the two samples were identical (Found: C, 68·9; H, 4·2. $C_{20}H_{13}NO_5$ requires: C, 69·2; H, 3·8%).

1,2,3,4-*Tetrahydro*-1-*hydroxyimino*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene*. A solution of the tetralone (VIII, 1 g) and hydroxylamine hydrochloride (1 g) in pyridine (4 ml) was heated at 100° on a steam bath for 5 hr and poured into water. Crystallization of the product from ethanol yielded the *oxime* (0·8 g) as needles, m.p. 191° (Found: C, 66·7; H, 4·4. $C_{18}H_{13}NO_5$ requires: C, 66·5; H, 4·6%). The oxime (0·8 g) was heated on a water bath for 1 hr with acetic anhydride (2 ml)

and pyridine (2 ml) and the solution left overnight at room temp. Dilution with water and crystallization of the product from ethanol gave the *acetate* (XI; 0·6 g) as prisms. m.p. 162° (Found: C, 65·5; H, 4·8. $C_{20}H_{17}NO_6$ requires: C, 65·4; H, 4·6%).

9-*Methyl*-6,7:2′,3′-*bismethylenedioxy*-1,2-*benzophenanthridine* (XII). A solution of the above oxime acetate (0·5 g) in acetic acid (2 ml) and acetic anhydride (3 ml) was saturated with dry hydrogen chloride at 0° and heated at 95–100° in a sealed tube for 8 hr. The contents were poured on ice and the brownish solid obtained was collected, washed with aqueous alcohol and basified with ammonia. Crystallization of the product from pyridine gave the *benzophenanthridine* (0·2 g) as needles, m.p. 299°, λ_{max} 230, 280, 350, 365 mμ (log ε 4·35, 4·70, 3·55, 3·35) (Found: C, 72·5; H, 4·1. $C_{20}H_{13}NO_4$ requires: C, 72·5; H, 3·9%).

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A list of some of the papers to be published in future issues

Contributed Symposia on Recent Developments in Organic Chemistry.
No. 2—New Reactions and New Classes of Compounds.

R. Huisgen, M. Seidel, G. Wallbillich und H. Knupfer: Diphenyl-nitrilinin und seine 1.3-Dipolaren Additionen an Alkene und Alkine.

R. W. White and W. D. Emmons: The chemistry of permaleic acid.

A. N. Nesmeyanov, R. Kh. Freidlina, E. C. Chukovckaya and R. G. Petrova: Addition, substitution and telomerization reactions of olefins of metal carbonyls or colloidal iron.

A. N. Nesmeyanov, R. Kh. Freidlina, V. N. Kost, T. T. Vassilyeva and B. V. Kopylova: Synthesis of α-chlorocarboxylic acids by chlorinating compounds containing the $CCl_2 - CH$ group in acid medium.

C. O. Parker, W. D. Emmons, H. A. Rolewicz, K. S. McCallum and A. S. Pagano: Chemistry of dinitroacetonitrile. Parts I—IV.

A. L. Nussbaum and C. H. Robinson: Some recent developments in the preparative photolysis of organic nitrites.

M. F. Hawthorne: Amine boranes—X. Alkylideneamino t-butylboranes. The hydroboration of nitriles with trimethylamine t-butylborane.

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